CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202971Orig1s000

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA 202-971

Sponsor:	Otsuka Pharmaceutical
Drug:	Aripiprazole extended release suspension for injection (Abilify Maintena)
Proposed Indication:	Schizophrenia
Material Submitted:	NDA Resubmission
Correspondence Date:	August 31, 2012
Date Received:	August 31, 2012
DARRTS SDN:	42
Sequence Number:	0037

I. Background

NDA 202-971 provides for a long-acting, intramuscular formulation of the atypical antipsychotic, aripiprazole, for the treatment of schizophrenia. The drug will be distributed in 300mg and 400mg kits which include a vial of drug product, a vial of sterile water for injection (SWFI) as diluent, syringes, needles, and a vial adapter. The approved tradename is Abilify Maintena.

This application was submitted on September 26, 2011, reviews were completed, and a Complete Response (CR) letter was issued on the PDUFA deadline, July 26, 2012. That letter indicated that we could not approve the application for marketing because of deficiencies in Current Good Manufacturing Processes at (b) (4), which manufactured the (b) (4) vials of SWFI intended to be included in the Abilify Maintena kits.

A Type A meeting with the sponsor was held on August 14, 2012, to consider two options: 1) elimination of the vial of SWFI from the kits and 2) substitution of the (b) (4) vial of SWFI from (b) (4) with a 5ml vial from another supplier, such as (b) (4). (According to the sponsor, no other supplier of (b) (4) vials of SWFI could be identified.) We had indicated that the second option was preferable to elimination of the vial from the kit because the lack of a vial of SWFI could result in either a delay of treatment or use of an inappropriate diluent in case no SWFI was available in the clinical setting. However, substitution of the 5ml vial would necessitate changes to the product labeling and possibly require an inspection of the facility that will manufacture the 5ml vial of SWFI.

Otsuka has now resubmitted the application and has selected (b) (4) as the new supplier of 5ml vials of SWFI to be included in the Abilify Maintena kits. Updated Chemistry, Manufacturing, and Controls information is provided in this

submission as well as updated labeling necessary due to replacement of the [redacted] vial with the [redacted] 5ml vial of SWFI. The User Fee due date will be February 28, 2013.

II. Review of Clinical Labeling

There are no new clinical data in this submission and product labeling will be substantially identical to that negotiated with the sponsor prior to the CR letter. Therefore, this review focuses on the labeling changes needed to accommodate the new 5ml vials of SWFI.

A. Labeling Changes

The sponsor has proposed a large number of changes to the product labeling. Most of these are editorial revisions in the following sections: 2.6, 5.5, 5.7, 6.1, 7.1, 8.1, 8.5, 8.6, 11, 12.3, and 14.

Substantive labeling changes germane to this resubmission are:

• section 2.4 states that a 5ml vial of SWFI will be used to withdraw water to reconstitute the drug product and that after withdrawal of the correct volume, a [redacted] volume will remain and should be discarded in the vial.
• section 2.5 repeats the information about the residual water.
• section 16.1 indicates that a 5ml vial of SWFI will be included in the 300mg and 400mg kits.
• section 16.2 provides information on the proper storage temperature.

B. Modifications to the Quick Reference Guides

The Quick Reference Guides that will be included in the 300mg and 400mg kits specify that 1) the kit contains a 5ml vial of SWFI, 2) there will be [redacted] excess water remaining in the vial after withdrawal of water for reconstitution of the product, and 3) this residual water should be discarded in the vial.

III. Conclusions and Recommendations

From a clinical standpoint, the revisions to sections 2.4, 2.5, and 16.1 of labeling, changes to the Quick Reference Guides, and editorial changes to labeling are acceptable and this application may be approved. Section 16.2 should be reviewed by the ONDQA review team.

Final approval of this application will depend on a satisfactory inspection of the [redacted] facility (if necessary) and recommendations from the ONDQA review team and the Office of Surveillance and Epidemiology, which will review the Quick Reference Guides, container label, and carton labeling.

Gregory M. Dubitsky, M.D.
September 28, 2012

cc: NDA 202-971
HFD-130/Dubitsky
/JZhang
/Mathis
/Laughren
/Saini

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GREGORY M DUBITSKY
09/28/2012

JING ZHANG
09/28/2012

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 25, 2012

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for complete response (CR) action for Abilify Maintena (aripiprazole) for the treatment of schizophrenia

TO: File NDA 202,971
[Note: This overview should be filed with the 9-26-11 original submission of this NDA.]

This memo is intended to change my recommendation for an approval action in my 7-24-12 memo to a complete response (CR) action. This change is based on new information that just came to my attention (see 7-25-12 memo from David Claffey). It has just been discovered that a manufacturing site (b) (4) for the vial of sterile water for injection that was to be part of the drug product kit was not entered into EES and was, therefore, unknown to CDER Office of Compliance (OC) at the time they made their "acceptable" recommendation. This site was inspected in June, 2012 and found to be unacceptable. Thus, OC has revised its recommendation to "withhold". Consequently, this NDA cannot be approved, and I will issue a CR letter, noting a deficiency at this site.

cc:
Orig NDA 202,971
HFD-130
HFD-130/TLaughren/MMathis/JZhang/GDubitsky/SSaini

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THOMAS P LAUGHREN
07/25/2012

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 24, 2012

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Abilify Maintena (aripiprazole) for the treatment of schizophrenia

TO: File NDA 202,971
[Note: This overview should be filed with the 9-26-11 original submission of this NDA.]

1.0 BACKGROUND

Abilify Maintena (aripiprazole) is a depot formulation of aripiprazole, an atypical antipsychotic, that is approved in other formulations for the treatment of schizophrenia, bipolar disorder, and the irritability of autism. Aripiprazole in oral formulations is also approved for the adjunctive treatment of MDD. This NDA, developed under IND 67,380, seeks a claim for a depot formulation for the treatment of schizophrenia, at doses of 300 or 400 mg, by intramuscular injection (gluteal) (b) (4). This claim is based on a single maintenance trial in patients with schizophrenia. This NDA was submitted on 9-26-11.

2.0 CHEMISTRY

This application was reviewed by David Claffey, Ph.D., from the CMC group, Jacqueline Ryan and QuynhNhu Nguyen from CDRH, and Jessica Cole from Microbiology. The original CMC review for this application could not recommend an approval (5-22-2012) because the microbiology review had not been completed and the Office of Compliance (OC) recommendations had not been made at that time. There was a problem with an alternative manufacturing site (b) (4) that was precluding an approval recommendation from Microbiology. This issue was subsequently resolved, once that site was withdrawn, and Microbiology has now completed its review with an approval recommendation (7-19-2012), based on findings from the primary manufacturing site. OC has also given an overall acceptable recommendation (7-20-2012).

The usability of this kit was reviewed by Yelena Maslow, Pharm.D. from DMEPA. She concluded that the kit can be adequately utilized for the recommended doses of 300 and 400 mg, but raised a concern about the lack of a kit specifically for delivering a 200 mg dose as needed in certain situations, e.g., poor 2D6 metabolizers. She also had other comments for the sponsor. We have discussed the question of a 200 mg kit internally, and decided that there is not really a compelling need for such a specialized kit. The sponsor has responded to Dr. Maslow's other comments, and these were satisfactory. Thus, DMEPA has also recommended approval.

Therefore, at this point, all CMC and device/human factors issues have been resolved.

3.0 PHARMACOLOGY

All of the nonclinical toxicology issues have been resolved.

4.0 BIOPHARMACEUTICS

Three clinical pharmacology trials were included as part of this NDA, i.e., a single dose in vivo release characteristics study (CN138-020), a single dose PK study (31-07-002), and a multiple dose PK study (31-07-244). The sponsor also submitted population PK analyses of their data and simulations to evaluate the impact of drug-drug interactions, missed doses and dose dumping. These data were reviewed by Huixia Zhang, Ph.D. and Satjit Brar, Ph.D. from OCP. They agreed that data from these trials and the efficacy and safety study (31-07-246) supported the proposed starting and maintenance doses, the 2 week oral supplementation at initiation of therapy, and the dose adjustments needed with 2D6 poor metabolizers, and when the depot is taken with strong 2D6 and 3A4 inhibitors. Use of the depot should be avoided in the presence of 3A4 inducers.

5.0 CLINICAL DATA

5.1 Efficacy Data

Given that aripiprazole is well-established and approved for the treatment of schizophrenia, we required only a single additional efficacy and safety study for this new formulation (31-07-246). The sponsor agreed to conduct a maintenance study to show that aripiprazole depot is able to delay time to relapse in schizophrenic patients who have been stabilized on this formulation, since the drug is most likely to be used for maintenance treatment. The study began with a screening phase to select schizophrenic patients for stabilization. These patients may have been on aripiprazole or another antipsychotic. For those not on aripiprazole, they were first converted to aripiprazole (phase 1). Patients were then stabilized on oral aripiprazole (10-30 mg/day) and had to meet stabilization criteria for at least 4 weeks (phase 2). Patients who met these criteria were then switched to aripiprazole depot 400 mg q month (phase 3). During phase 3, patients

were treated with oral aripiprazole 10-20 mg/day for the first 2 weeks, to allow the depot to achieve therapeutic levels. In addition, patients could have their dose reduced to 300 mg q month. Patients who met stability criteria on aripiprazole depot for 12 weeks could be randomized to continued depot (at their optimal dose) or placebo (2:1 randomization) to observe for relapse (phase 4). Time to relapse was the primary endpoint, and percentage relapse was the key secondary. 403 patients were randomized in phase 4; their mean PANSS total score was 55 and mean CGI-severity was 2.9. The SAP called for two interim analyses, based on occurrence of either 50% or 75% of the targeted 125 events (with stopping rules). The results, after the first interim analysis, were highly favorable to drug (HR 0.2), and met criteria for stopping. For the final analysis, the HR was 0.2 ($P < 0.0001$). Relapse percentages were 10% for drug and 40% for placebo. There were, however, concerns about data from 2 sites: 046 identified as problematic by the sponsor and site 002 identified as problematic by OSI. The efficacy analysis was repeated without data from these 2 sites, and the results were still highly significant in favor of drug.

These data were reviewed by Greg Dubitsky, M.D. from the clinical group and Andrejus Parfionoval, Ph.D. from the biometrics group. Both agreed that this study supports the sponsor's claim, as did Jing Zhang, M.D., clinical team leader, and I do as well. A full pediatric waiver was granted given that use of this formulation would be expected to be quite unusual in pediatric patients.

5.2 Safety Data

The safety data for this NDA were derived from 3 PK studies (very limited contribution) and mostly from 7 large phase 3 trials. In addition to the placebo-controlled study that was most important for the US application (31-07-246), there were 2 large active-controlled trials for EMA registration (31-07-247 and 31-08-003). In addition, there were 4 large open label uncontrolled safety trials (31-08-248, 31-10-270, 31-10-002, and 31-11-283). Safety data were available for a total of n=1324 patients receiving at least one dose of the depot formulation, and from n=1287 patients who received one or more IM doses of 300 or 400 mg q month (a total of 1281 patient years). These included 832 patients who received monthly depot injections for at least 6 months and 630 for at least 12 months. The safety profile for the depot formulation of aripiprazole was similar to that seen with the oral formulation, with the exception of injection site adverse events that are expected for a depot formulation. There were 12 deaths in patients taking the depot formulation, however, these were of widely varying causes, and all could most reasonably be considered causally related to underlying disease, e.g., cancer, heart disease, the schizophrenic illness (suicide), or unrelated causes (e.g., homicide). There were no unexpected findings and no new findings of concern. Thus, the safety findings of aripiprazole depot can be adequately characterized in labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have now reached final agreement with the sponsor on labeling.

6.0 FOREIGN REGULATORY ACTIONS

To my knowledge, aripiprazole depot is not approved anywhere at this time for the treatment of schizophrenia.

7.0 LABELING AND APPROVAL LETTER

7.1 Labeling

As noted, we have now reached final agreement with the sponsor on labeling.

7.2 AP Letter

The AP letter includes the agreed upon final labeling.

8.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Otsuka has submitted sufficient data to support the conclusion that aripiprazole depot is effective and acceptably safe in the treatment of schizophrenia, and we have reached final agreement with the sponsor on labeling. Thus, we will issue an approval letter with the agreed upon final label.

cc:
Orig NDA 202,971
HFD-130
HFD-130/TLaughren/MMathis/JZhang/GDubitsky/SSaini

DOC: Aripiprazole_Depot_Laughren_AP_Memo.doc

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/s/

THOMAS P LAUGHREN
07/24/2012

Addendum to the Review and Evaluation of Clinical Data
NDA #202,971

Sponsor:	Otsuka
Drug:	Aripiprazole IM Depot (Abilify Maintena)
Proposed Indication:	Schizophrenia
Material Submitted:	Final Safety Update
Correspondence Date:	May 22, 2012
Date Received:	May 23, 2012
Serial Number:	0024
DARRTS SDN:	24

I. Background

Otsuka submitted this New Drug Application (NDA) on September 26, 2011, to obtain marketing approval for an extended release suspension of aripiprazole for intramuscular injection (tradename Abilify Maintena) in the treatment of schizophrenia. The cutoff date for safety data in that original submission was January 7, 2011.

The 120-Day Safety Update to the application was submitted on January 23, 2012, with a safety cutoff date of August 15, 2011. I completed my review of this NDA on May 29, 2012. That review encompassed both the original submission and the 120-Day Safety Update.

This submission contains a Final Safety Update, with a cutoff date of January 16, 2012. This addendum to my May 29, 2012, clinical review is intended to address this update.

II. Clinical Review of Final Safety Update

A. Clinical Trials

This update includes safety data from 4 clinical studies which were ongoing as of the 120-Day Safety Update. These 4 studies are summarized below.

- 31-07-247 - stabilization of schizophrenic patients on oral aripiprazole followed by 2:2:1 randomization to 38 weeks of aripiprazole IM depot 300 or 400mg q4 weeks, aripiprazole IM depot 50 or 25mg q4 weeks, or oral aripiprazole 10 to 20 mg/day to demonstrate non-inferiority of IM depot versus oral aripiprazole as maintenance treatment.
- 31-08-003 - stabilization of schizophrenic patients on oral aripiprazole followed by 1:1 randomization to 26 weeks of aripiprazole IM depot 300 or 400mg q4

weeks or oral aripiprazole 6-24 mg/day to demonstrate non-inferiority of IM depot versus oral aripiprazole as maintenance treatment.

- 31-08-248 - 52 week open-label study enrolling *de novo* patients and rollover patients from trials 31-07-246 or 31-07-247.
- 31-10-270 - open-label extension study for patients who completed 31-08-248.

In addition, safety data from 2 studies that were initiated since the last update are contained in this update. These 2 new studies are described below

- 31-10-002 - open-label, multiple dose clinical pharmacology trial in Japan to evaluate the pharmacokinetics and safety of aripiprazole IM depot 300 and 400mg IM monthly in patients with schizophrenia.
- 31-11-283 - Phase 3, open-label study in the U.S. to assess inpatient psychiatric hospitalization rates in patients receiving standard oral antipsychotic treatment for 6 months (historically) versus rates in patients after switching to once monthly aripiprazole IM depot injections for 6 months (prospectively). Patients completing this study could enter an open-label extension trial.

All 6 studies were ongoing as of January 16, 2012.

Because aripiprazole IM depot is not marketed in any country, no postmarketing safety data with this product are available.

B. Cumulative Patient Exposure

The cumulative number of patients exposed to aripiprazole IM depot by study type as of January 16, 2012, is displayed in Table 1 below.[1]

Table 1: Number of Patients Exposed to Aripiprazole IM Depot By Study Type

Clinical Trials	Subjects Exposed
PHASE 1 TRIALS	
SINGLE DOSE TRIALS	46
MULTIPLE DOSE TRIALS	45
PHASE 3 TRIALS	
PLACEBO-CONTROLLED TRIAL (31-07-246)	576[2]
All PHASE 3 TRIALS	1,233
TOTALS	
ALL TRIALS (PHASE 1-3)	1,324
ALL TRIALS DOSED WITH 300-400mg	1,287

[1] Trials 31-07-247 and 31-08-003 are not included in these and the following figures because both trials remained blinded as of the Final Safety Update cutoff date.
[2] This number includes patients who received open-label IM depot in study 31-07-246.

As of January 16, 2012, a cumulative total of 1,324 patients had been exposed to aripiprazole IM depot in clinical trials, of which 1,233 patients participated in Phase 3 trials. There were 1,287 patients who received one or more IM doses of 300mg or 400mg, yielding a total of 1,281 patient-exposure years.

Across all trials as of the above cut-off date, 832 patients received aripiprazole IM depot 300mg or 400mg for at least 6 continuous months (7 consecutive injections) and 630 received injections of 300mg or 400mg for at least 12 continuous months (13 consecutive injections).

C. Safety Findings

This review focused on serious adverse events (including deaths) and adverse events that led to dropout in the above 6 trials during the interval covered by this update.

Deaths

There was only one newly reported death:

Patient 10270-206-0794 from study 31-10-270 was a 36 year old male who was receiving aripiprazole IM depot 400mg. He decided to get a haircut in preparation for his next study visit. After the haircut, his neighbor told him that the haircut was bad, prompting the patient to return to his barber, where they quarreled. The patient stabbed the barber to death and turned himself in to the police. While in police custody, the brother of the dead barber visited the patient under the pretext of being a friend bringing food. During the visit, the barber's brother shot the patient in the face, killing him. The patient died on day (b) (6) of the study.

There is insufficient evidence to conclude that this patient's aggressive behavior was a reaction to aripiprazole IM depot treatment.

Non-Fatal Serious Adverse Events

Newly reported non-fatal serious adverse events in patients who received aripiprazole IM depot are listed in the Appendix to this review.

By far, the most commonly reported serious adverse event was exacerbation of schizophrenia or psychosis. These events most likely represent worsening of the underlying illness as opposed to a reaction to aripiprazole IM depot injections.

There was only one serious adverse event which I regard as possibly attributable to aripiprazole IM depot: Patient 08003-403-0323 in trial 31-08-003 was a 26 year old male who had taken oral aripiprazole (up to 24 mg/day) for about 2 months before his first injection of aripiprazole IM depot 400mg. About 6 weeks later, he experienced a persistent and painful penile erection, which was reported

by his grandmother. The event did not respond to intravenous diazepam and the patient was hospitalized. A CBC and chest X-ray were normal. He received oral diazepam, the antispasmodic drug hyoscine butylbromide, and chlorpromazine. The priapism resolved 12 days later and the patient was discharged. No further study drug was administered. Priapism has been reported in previous clinical trials with aripiprazole at a frequency of less than 1/1,000 patients.[3]

Dropouts Due To Adverse Events

My examination of newly reported non-serious adverse events that led to dropout among patients treated with aripiprazole IM depot revealed no events that were unexpected and clinically significant. The most commonly reported events that led to discontinuation were exacerbation of schizophrenia and akathisia.

III. Literature Search

No literature search was reported by the sponsor as part of the Final Safety Update.

On June 14, 2012, I conducted a search of the literature since April 27, 2012 (the cutoff date for the search I conducted as part of my original review), for articles which described safety findings with the IM depot formulation of aripiprazole. This search utilized PubMed and the search string "aripiprazole depot." No new articles were identified.

However, I am aware of one very recently published article by Kane and colleagues that described the results of trial 31-07-246.[4] No new safety findings were mentioned in this article.

IV. Conclusions

The data reported in this Final Safety Update are consistent with the safety information contained in the original submission and 120-Day Safety Update. I identified no new findings that would impact on the approvability of this application or require substantial changes to product labeling.

Gregory M. Dubitsky, M.D.
June 14, 2012

[3] See the currently approved Abilify labeling.
[4] Kane JM, et al. Aripiprazole Intramuscular Depot as Maintenance Treatment in Patients With Schizophrenia: A 52-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Psychiatry 2012;73(5):617-624.

APPENDIX

NEWLY REPORTED NON-FATAL SERIOUS ADVERSE EVENTS ASSOCIATED WITH ARIPIPRAZOLE IM DEPOT TREATMENT	
Trial/SAE	**Number of Patients Reporting SAE**
31-08-248	
Schizophrenia or psychotic disorder	5
Genital candidiasis	1
Intentional overdose	1
Pneumonia, atrial fibrillation, & hypertension	1
Dehydration	1
Open angle glaucoma	1
Facial pain	1
Anxiety	1
Congenital anomaly (club feet)	1
Cellulitis & gangrene (big toe of left foot)	1
31-10-270	
Schizophrenia or psychotic disorder	3
Ovarian cyst, influenza, & pneumonia	1
Salivary gland adenoma	1
Pulmonary tuberculosis	1
Suicide attempt	1
31-11-283	
Psychosis	3
Suicide attempt	1
Gastritis	1
31-07-247	
Schizophrenia	1
Suicide attempt	1
31-08-003	
Schizophrenia	2
Suicide attempt	1
Induced abortion	1
Priapism	1
Mental instability (stealing & delusional)	1

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GREGORY M DUBITSKY
06/14/2012

JING ZHANG
06/16/2012

CLINICAL REVIEW

Application Type	NDA
Application Number	202971
Priority or Standard	Standard
Submission Date	September 26, 2011
Received Date	September 26, 2011
PDUFA Goal Date	July 26, 2012
Division/Office	DPP/ODE1
Reviewer Name	Gregory Dubitsky, M.D.
Review Completion Date	May 29, 2012
Established Name	Aripiprazole for extended release injectable suspension
Trade Name	Abilify Maintena
Therapeutic Class	Antipsychotic
Applicant	Otsuka Pharmaceutical
Formulation	Powder for suspension
Dosing Regimen	300 or 400mg IM (b) (4)
Indication	Schizophrenia
Intended Population	Adults

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1 RECOMMENDATIONS/RISK-BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

From a clinical standpoint, it is recommended that this application be approved.

1.2 Risk-Benefit Assessment

The risks associated with Abilify Maintena treatment appear to be the same as those with the marketed oral formulations of aripiprazole. The therapeutic efficacy is expected to be comparable as well. Abilify Maintena offers the added benefits of convenience of administration and assured delivery of drug. Therefore, for patients with schizophrenia being treated with aripiprazole and especially for patients with poor compliance, the benefits of Abilify Maintena therapy outweigh the risks.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

The sponsor contends that there is no risk associated with Abilify Maintena therapy that would require a Risk Evaluation and Mitigation Strategy (REMS). It is felt that the following will be adequate to monitor the safety of aripiprazole IM depot treatment:

- an ongoing pharmacovigilance plan that includes systematic collection of adverse event information, real time and periodic assessment of single and aggregate safety reports to identify potential signals, and submission of aggregate reports as required by regulations.
- the sponsor recommends that the Medication Guide be distributed to outpatients at the time of first injection, upon request at subsequent injections, and after any material change to the document. There would be no requirement for distribution to inpatients, in accordance with draft guidance from the Agency.[1] However, the Medication Guide would be distributed to any inpatient who requests it.

I agree that there appear to be no significant safety concerns with Abilify Maintena that would require a REMS. Comments from the Division of Risk Management are pending at this time.

1.4 Recommendations for Postmarketing Requirements and Commitments

There are no recommendations for Postmarketing Requirements or Commitments at this time. A full pediatric waiver has been granted.

[1] U.S. Food and Drug Administration. Draft Guidance for Industry: Medication Guides - Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), February 2011.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Aripiprazole is a second generation antipsychotic that has been widely used since its initial approval in 2002 for the treatment of schizophrenia. The current approved indications for oral formulations of aripiprazole include: treatment of schizophrenia; acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate; maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate; adjunctive treatment of major depressive disorder; and treatment of irritability associated with autistic disorder. The current approved indication for the immediate-release injectable formulation of aripiprazole is treatment of acute agitation associated with schizophrenia or bipolar I disorder.

2.2 Currently Available Treatments for Proposed Indications

Both typical and atypical antipsychotics may be used for the maintenance treatment of schizophrenia. Several of these agents are available in an extended-release injectable form in the United States:

- haloperidol decanoate (Haldol Decanoate) (NDA 18-701).
- fluphenazine decanoate (ANDA 71-413).
- risperidone (Risperdal Consta) (NDA 21-346).
- paliperidone palmitate (Invega Sustenna) (NDA 22-264).
- olanzapine pamoate (Zyprexa Relprevv) (NDA 22-173).

2.3 Availability of Proposed Active Ingredient in the United States

Aripiprazole is currently available in tablet (NDA 21-436), oral solution (NDA 21-713), orally disintegrating tablet (NDA 21-729), and immediate-release injectable formulations (NDA 21-866).

2.4 Important Issues With Consideration to Related Drugs

Other atypical antipsychotic drugs carry a risk of metabolic effects, such as weight gain and hyperglycemia. In addition, Zyprexa Relprevv may cause severe sedation or delirium after injection and patients receiving this drug must be observed for 3 hours post-injection in a registered facility with emergency response capabilities.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On March 4, 2003, the Division held a pre-IND meeting with representatives from Otsuka Pharmaceuticals and Bristol Myers Squibb to discuss their proposed development program for an IM depot formulation of aripiprazole. During that meeting, we indicated that non-inferiority trials, as proposed by the sponsor at that time, would not be acceptable to provide primary evidence of efficacy. We recommended three alternatives: 1) a trial that included an ersatz placebo control, 2) a trial to show superiority over an active control, or 3) a relapse prevention trial to demonstrate a maintenance effect. IND 67,380 was submitted on May 12, 2003, to provide for the conduct of studies to support a future NDA for aripiprazole IM depot in the maintenance treatment of schizophrenia.

A pre-NDA meeting was held between the Division of Psychiatry Products (DPP) and representatives of Otsuka Pharmaceuticals on June 7, 2011. The purpose of this meeting was to discuss the nonclinical and clinical development program results and receive FDA feedback on the proposed NDA for aripiprazole intramuscular (IM) depot for the maintenance treatment of schizophrenia. The discussion at this meeting encompassed the adequacy of the clinical development program, plans to utilize an eCTD format, advice on a proposed Integrated Safety Summary (ISS), a request for an analysis of data from the Columbia-Classification Algorithm for Suicide Assessment (C-CASA), the sponsor's plans to request a waiver of PREA requirements, and the need for case report forms from studies that remained blinded. Additionally, we informed the sponsor of anticipated problems with the syringe intended for marketing as part of the aripiprazole IM depot kit. For example, we had received numerous reports of the needle/collar/syringe unit becoming loose in patients who were administered another product, [redacted] (b) (4), with the needle remaining in the patient after administration of drug or of healthcare providers being stuck with dislodged needles. The sponsor was informed of the need to address this concern.

This application was submitted and received on September 26, 2011. A filing meeting was held on November 14, 2011. The sponsor was notified on November 21, 2011, that this application was filed.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

I audited case report forms (CRF's) to evaluate the consistency of adverse event information across the CRF, narrative summary, and adverse event tabulation (ae.xpt) data for a sample of patients. CRF's for approximately 223 patients were provided in the original submission. Most of these (N=215) came from either study 31-07-246 or 31-08-248. A 5% sample of all CRF's (N=11) was randomly selected for this audit. Data for the following 11 patients were audited:

Study	Center	Patient
246	0006	0408
246	0019	0165
246	0032	0471
246	0038	0972
246	0127	0626
246	0217	0866
248	0103	0964
248	0115	0637
248	0220	0762
248	0806	4001
248	0871	4163

The adverse event information was found to be consistent across the above three documents for these patients.

In addition, I audited the coding of reported adverse event terms to MedDRA preferred terms for trials 31-07-246 and 31-08-248. The adverse event tabulations (ae.xpt) for each study were examined, comparing the variables AETEXT (investigator term) versus PT_TEXT (MedDRA preferred term) for each trial. No coding deficiencies were detected.

3.2 Compliance with Good Clinical Practices

The Office of Scientific Investigations (OSI) was consulted to inspect three of the clinical sites from the key efficacy trial, 31-07-246, based on high subject enrollment at those sites: site #002 (Arifulla Khan, M.D., of Bellevue, WA), site #007 (Mark Lerman, M.D., of Hoffman Estates, IL), and site #218 (Ahmad H. Sulaiman, M.D., of Kuala Lumpur, Malaysia). A Clinical Inspection Summary from John Lee, M.D., OSI Medical Officer, is pending at this time.

All clinical trials were conducted in compliance with ICH Good Clinical Practice guidelines.

Otsuka certified that it did not use and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

The sponsor requested statements of financial interests from a total of 109 principal investigators for the covered trial 31-07-246. As of August 5, 2011, all 109 principal investigators had responded. Two principal investigators had financial interest information to disclose:

- [redacted] (b) (6)
- [redacted] (b) (6)

It does not appear that patients from either site entered the randomized, double-blind phase of this trial. Therefore, the potential impact of these sites on the efficacy results of the trial is felt to be minimal.

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The Chemistry, Manufacturing and Controls data were reviewed by David J. Claffey, Ph.D., and documented in a May 22, 2012, review. Dr. Claffey reported no clinically significant CMC issues with this application. However, he could not yet recommend approval because the microbiology review and Office of Compliance review have not been received.

4.2 Clinical Microbiology

The clinical microbiology review is being conducted Jessica G. Cole, Ph.D. That review has not yet been finalized.

4.3 Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review is being performed by Sonia Tabacova, M.D., Ph.D. Dr. Tabacova reports no significant issues with this application.

4.4 Clinical Pharmacology

4.4.3 Pharmacokinetics

The clinical pharmacology review of this application is being completed by Huixia Zhang, Ph.D., and Satjit Brar, Pharm.D., Ph.D.

The clinical pharmacology review team has made a few suggestions for labeling with respect to dosing recommendations, for example dosing in CYP2D6 poor metabolizers. Their recommendations will be incorporated into our proposed labeling.

4.5 Center for Devices and Radiological Health

4.5.1 Combination Product Review

Jacqueline S. Ryan, M.D., Combination Products Team Leader, reviewed the safety needles, plastic syringe, and vial adapter that will be included in the aripiprazole IM depot injection kits. Clarification of the Needle-Pro device to be used in the kits has been requested from Otsuka given that Smiths Medical does not currently market the 21 gauge x 2 inch version of the Needle-Pro device. This review has not yet been finalized.

4.5.2 Human Factors Review

QuynhNhu Nguyen, Biomedical Engineer/Injection Systems Human Factors Specialist from the Center for Devices and Radiological Health (CDRH), completed a human factors review of the aripiprazole IM depot kit on March 5, 2012.

Human factor considerations for the use of the IM depot kit include the following:

• the primary user will be a healthcare professional.
• the kit will be used primarily in a clinical environment.
• it is not expected that users will receive any formal training. Users are expected to use the enclosed Instructions for Use and Quick Reference Guide.
• expected user tasks are selecting the correct dose kit for a particular patient, determining the correct volume of diluent for drug reconstitution, drawing diluent into the syringe, injecting diluent into the drug vial, shaking the drug vial to attain a homogeneous mixture, determining the correct amount of drug suspension to withdraw for injection, selecting the appropriate needle length for injection, and selecting the body site for injection.

A use-related risk assessment was utilized to identify risks associated with user interaction with the kit. Based on this assessment, three critical tasks that could cause dosing errors were identified: determination of the correct volume of diluent, determination of the amount of suspension to withdraw for injection, and selecting the appropriate needle length.

In the validation study, there were four use errors among two participants in the validation study, which also included 16 nurses and nurse practitioners: one subject, who refused to read the directions, assumed that all diluent was required, failed to use the vial adapter, and did not follow guidance on choosing a needle size. The other subject did not withdraw the correct volume of suspension.

Based on these data, Ms. Nguyen requested further information from the sponsor, specifically: 1) submission of the comprehensive use-related risk

assessment utilized to identify critical tasks, 2) consideration of whether the errors made by the two subjects in the validation study are likely to be repeated by other users and, if so, corrective steps to reduce or eliminate this risk, and 3) details of plans to provide additional support through their commercial operations to healthcare providers to minimize the risk of a dosing error.

This review has not yet been finalized.

4.6 Office of Surveillance and Epidemiology

4.6.1 Division of Medication Error Prevention and Analysis

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted to assess 1) the proposed proprietary name (Abilify (b) (4)) and 2) the usability study and other components of this product.

Loretta Holmes, B.S.N., Pharm.D., completed the proprietary name review on May 21, 2012. Initially, she had concluded that the proposed name, Abilify (b) (4), was unacceptable because (b) (4) The sponsor subsequently proposed Abilify Maintena and this name was deemed to be acceptable.

Yelena Maslov, Pharm.D., reviewed the usability study submitted on December 21, 2011, as well as product design, vial labels, carton, prescription information, instructions for use, and quick reference guide for the potential to contribute to medical errors. Her recommendations are conveyed in her review dated May 18, 2012, and include a recommendation that the sponsor develop a 200mg strength kit because it is unknown whether healthcare practitioners could correctly administer this dose with the instructions provided.

4.6.2 Division of Risk Management

The Division of Risk Management (DRISK) was consulted to evaluate the risk management plan and medication guide for this product. Their review is pending.

4.7 Office of Biometrics

Andrejus Parfionovas, Ph.D., conducted the statistical review of trial 31-07-246, the key efficacy trial in this application. He confirmed that adequate evidence of the efficacy of aripiprazole IM depot in the maintenance treatment of schizophrenia has been presented to support marketing approval. His final review is pending.

5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

This application was submitted on September 26, 2011. The cutoff date for safety data in that original submission was January 7, 2011. The 120-Day Safety Update was submitted on January 23, 2012, with a cutoff date of August 15, 2011.

The aripiprazole IM depot development program consists of eight studies:

Phase 1 Clinical Pharmacology Trials

- CN138-020 - in vivo release characteristics of single dose aripiprazole IM depot (15, 50, 100, 200, 300, and 400mg).
- 31-07-002 - single dose PK and tolerability (100, 200, 300, and 400mg).
- 31-05-244 - multiple dose PK & tolerability (200, 300, and 400mg q4 weeks for 5 months).

These three trials were conducted in patients with schizophrenia or schizoaffective disorder. All were complete as of the safety cutoff date for the original application submission.

Controlled Phase 3 Trials

- 31-07-246 - stabilization of schizophrenic patients on aripiprazole IM depot for 12 weeks followed by 2:1 randomization to aripiprazole IM depot (300 or 400mg q4 weeks) or IM depot placebo for 52 weeks. This is the pivotal efficacy study for this NDA.
- 31-07-247 - stabilization of schizophrenic patients on oral aripiprazole followed by 2:2:1 randomization to 38 weeks of aripiprazole IM depot 300 or 400mg q4 weeks, aripiprazole IM depot 50 or 25mg q4 weeks, or oral aripiprazole (10-20 mg/day) to demonstrate non-inferiority of IM depot versus oral aripiprazole as maintenance treatment.
- 31-08-003 - stabilization of schizophrenic patients on oral aripiprazole followed by 1:1 randomization to 26 weeks of aripiprazole IM depot (300 or 400mg q4 weeks) or oral aripiprazole (6-24 mg/day) to demonstrate non-inferiority of IM depot versus oral aripiprazole as maintenance treatment.

Trial 31-07-246 was complete as of the cutoff date for the original application submission. The other two trials were ongoing and blinded as of the cutoff date for the 120-Day Safety Update.

Open-label uncontrolled trials

- 31-08-248 - 52 week open-label study enrolling *de novo* patients and rollover patients from 31-07-246 or 31-07-247.

• 31-10-270 - open-label extension study for patients who completed 31-08-248.

Both studies were ongoing as of the cutoff date for the 120-Day Safety Update.

An enumeration of subjects exposed to aripiprazole IM depot in these trials as of August 15, 2011, is provided in Table 1. Trials 31-07-247 and 31-08-003 are not included in this enumeration as both remained blinded as of the cutoff date.

Table 1: Numbers of Patients Exposed to Aripiprazole IM Depot By Study Type as of August 15, 2011

Clinical Trials		Subjects Exposed
PHASE 1/CLINICAL PHARMACOLOGY		
SINGLE DOSE	CN138-020	20
	031-07-002	26
MULTIPLE DOSE	31-05-244	39
PHASE 3 TRIALS		
PLACEBO-CONTROLLED	31-07-246	576
OPEN-LABEL, UNCONTROLLED	31-08--248	928
	31-10-270	148
TOTALS		
ALL TRIALS		1190
ALL MULTIPLE DOSE TRIALS		1144
ALL PHASE 3		1105
ALL DOSE 300-400mg		1153

5.2 Review Strategy

The efficacy review of this application focused on trial 31-07-246 because this was the only adequately designed trial in the development program to demonstrate effectiveness.

The safety review examined deaths, non-fatal serious adverse events, and dropouts due to adverse events from all eight studies in the development program. There were no trials suitable for standard safety analyses, i.e., randomized, placebo-controlled trials. Therefore, analyses of changes in laboratory parameters, vital signs, and ECG measures were examined within the IM Depot Stabilization Phase of trial 31-07-246 to evaluate safety findings immediately after patients began treatment with this product.

Although trial 31-07-246 entailed a randomized, placebo-controlled phase, analyses based on this phase are problematic because it included only patients who had tolerated and experienced a response to several weeks of treatment with both oral and IM depot aripiprazole. In addition, there was a substantial difference in follow-up times between the drug and placebo treatment groups during this phase, making a comparison of safety between the treatment groups

unreliable. Therefore, the safety analyses that used these data are considered misleading for purposes of labeling.

The following sections are omitted from this review because either they do not apply to the evaluation of this product or there was no new information provided: 4.4.1 (Mechanism of Action), 4.4.2 (Pharmacodynamics), 7.5.2 (Time Dependency), 7.5.4 (Drug-Disease Interaction), 7.5.5 (Drug-Drug Interaction), and 7.6.1 (Human Carcinogenicity).

6 REVIEW OF EFFICACY

Efficacy Summary

Study 31-07-246 provided adequate evidence of the efficacy of aripiprazole IM depot injection 300mg or 400mg every 4 weeks in the maintenance treatment of patients with schizophrenia.

6.1 Studies Pertinent to Maintenance Treatment of Schizophrenia

6.1.1 Rationale for Selection of Studies for Review

Only study 31-07-246 was adequately designed to provide evidence of efficacy to support a marketing claim.

6.1.2 Study Summaries

Study 31-07-246

Methods/Study Design/Analysis Plan

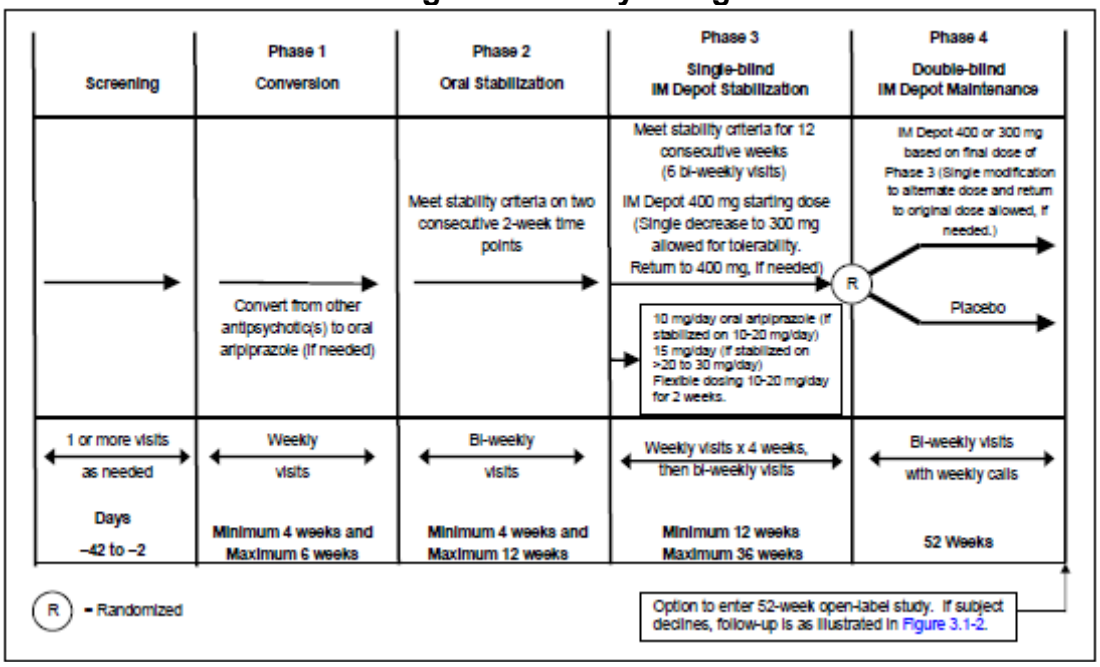
Study Objective

The primary study objective was to compare the efficacy of aripiprazole IM depot with placebo IM depot in patients with schizophrenia who had maintained stability on aripiprazole IM depot for at least 12 weeks.

Study Design

Study 31-07-246 consisted of a screening phase and four treatment phases. These are depicted in Figure 1 below.

Figure 1: Study Design



After screening, subjects receiving an antipsychotic drug other than aripiprazole entered Phase 1 where they were cross-titrated to oral aripiprazole over 4 to 6 weeks. The cross-titration scheme was decided by the investigator, with the goal of achieving an oral aripiprazole daily dose of 10mg or 15mg at the end of Phase 1. Subjects already receiving aripiprazole monotherapy at screening entered the study at Phase 2.

During Phase 2, patients were stabilized on an oral dose of aripiprazole in the range from 10 to 30 mg/day. Stability was defined as fulfilling the following criteria:

1) outpatient status
AND
2) PANSS total score ≤80
AND
3) PANSS score ≤4 on each of the following items:
-conceptual disorganization.
-suspiciousness.
-hallucinatory behavior.
-unusual thought content
AND
4) CGI severity score ≤4 (moderately ill)
AND
5) CGI-SS ≤2 (mildly suicidal) on Part 1 and ≤5 (minimally worse) on Part 2.

At the final Phase 2 visit, patients meeting these criteria for 4 consecutive weeks (2 consecutive biweekly visits) received single-blind aripiprazole IM depot 400mg, regardless of the Phase 2 oral dose, in addition to oral aripiprazole 10 to 20 mg/day for the first 2 weeks of Phase 3 to maintain therapeutic plasma levels. The Phase 3 oral dose was based on the last Phase 2 oral dose as follows:

• patients with a Phase 2 stabilization dose of 10 to 20 mg/day, inclusive, received 10 mg/day for the first 2 weeks of Phase 3.
• patients with a Phase 2 stabilization dose of >20 to 30 mg/day received 15 mg/day for the first 2 weeks of Phase 3.

The investigator had the option of increasing the Phase 3 oral dose to 20 mg/day or decreasing it to 10 mg/day at any time during the first 2 weeks of Phase 3, depending on clinical need. Regarding the aripiprazole IM depot dose, a single decease to 300mg was allowed during Phase 3 if the 400mg dose was not well-tolerated. A single return to 400mg was also allowed, if clinically indicated.

The IM depot dose was administered into the gluteal muscle using a 21 gauge needle, either 1.5 or 2 inches long. Needle length was determined by the individual patient's BMI: for patients with a BMI ≤28 kg/m^2, a 1.5 inch needle was used and for those with a BMI >28 kg/m^2, a 2 inch needle was used.

The first Phase 3 visit at which the patient met the above five stability criteria marked the beginning of a stability period. Stabilization for 12 consecutive weeks (6 consecutive biweekly visits), with one allowed excursion that was not at the end of the stability period, was required for entry into Phase 4.

In Phase 4, patients were randomized in a 2:1 ratio to one of the following double-blind treatments:

• continued treatment with aripiprazole IM depot (300 or 400mg).
• placebo IM depot (without a taper).

The Phase 4 starting dose was the last IM depot dose in Phase 3. During Phase 4, the 400mg dose could have been decreased to 300mg once and increased back to 400mg once. Likewise, the 300mg dose could have been increased to 400mg once and decreased back to 300mg once. Injections continued every 4 weeks for the remainder of the trial. During Phases 3 and 4, a Site Study Drug Manager prepared and administered the IM depot injections due to differences in the appearance of the reconstituted aripiprazole (milky white suspension) versus placebo (clear solution).

Other antipsychotic drugs, antidepressants, mood stabilizers, CYP3A4 inducers, and CYP3A4 or CYP2D6 inhibitors were prohibited during Phases 2, 3, and 4. Benzodiazepines were allowed to a maximum of 6 mg/day of lorazepam or equivalent but not within 8 hours of any rating scale administration.

Trial Population
This trial was conducted in the U.S., Mexico, Argentina, Bulgaria, Romania, Serbia, Slovakia, Russia, India, Taiwan, Malaysia, and the Philippines at 108 trial centers in 843 patients. Forty-two of these sites were in the United States and enrolled 392 patients.

The trial population was comprised of adults (ages 18 to 60 years) with a DSM-IV-TR diagnosis of schizophrenia for at least 3 years currently treated with one or more antipsychotics other than clozapine. Patients must have had a history of symptom exacerbation with interruption or discontinuation of antipsychotic treatment. Patients with other current DSM-IV-TR diagnoses and those deemed to be at significant risk of violent behavior or suicide as well as those with current substance abuse (excluding nicotine and caffeine) were excluded. It was planned that about 1500 patients would be enrolled from an estimated 120 sites worldwide.

Clinical Assessments
Efficacy assessments included the PANSS and CGI. During the IM Depot Stabilization Phase, these evaluations were conducted at weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, and 36. During the IM Depot Maintenance Phase, these assessments were performed at weeks 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, and 52.

Efficacy Analysis
Efficacy analyses were based on the intent-to-treat (ITT) dataset, defined as all patients randomized to double-blind treatment in Phase 4. The primary efficacy endpoint was time from randomization to exacerbation of psychotic symptoms/impending relapse in Phase 4. Exacerbation/impending relapse was defined as meeting any or all of the following 4 criteria:

1) CGI improvement score ≥5 (minimally worse) AND one of the following two criteria: a) an increase in any of the following PANSS item scores to a score >4 with an absolute increase ≥2 on that item since randomization: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content OR b) an increase on any of these items to a score >4 and an absolute increase ≥4 on the combined score of these items since randomization
OR
2) hospitalization due to worsening of psychotic symptoms (including partial hospitalization) but excluding hospitalization for psychosocial reasons
OR
3) CGI-SS score of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2
OR

4) violent behavior resulting in clinically significant self-injury, injury to another person, or property damage.

The appearance of relapse resulted in withdrawal from the study for lack of efficacy.

Interim analyses of efficacy were planned when approximately 50% and 75% of events were accrued. Based on relapse rates in a similar trial with oral aripiprazole and sample size computations, it was projected that a total of 125 impending relapse events would occur in this trial. Thus, interim analyses were planned after the 63rd and 94th cases of impending relapse. The objective of these analyses was to determine if there was sufficient evidence of efficacy to merit premature termination of the trial. Thus, the primary endpoint (time from randomization to impending relapse) was analyzed by comparing the aripiprazole and placebo groups using the log-rank test at a two-sided alpha level of 0.001 and Haybittle-Peto boundaries for rejection of the null hypothesis. These boundaries provided for an alpha level of 0.001 for each interim analysis and an alpha level of 0.0498 for the final analysis. These analyses were conducted by an independent unblinded Data Analysis Center in coordination with a Data Monitoring Committee (DMC).

Time to exacerbation/impending relapse was tested using the log-rank test to compare the Kaplan-Meier survival curves for the aripiprazole and placebo treatment groups at an overall two-sided alpha level of 0.05.

The key secondary efficacy endpoint was the percentage of patients meeting criteria for exacerbation of psychotic symptoms/impending relapse during Phase 4. To preserve the Type I error rate at 0.05, the key secondary analysis would be performed only if the primary analysis was positive at a 0.05 level. The chi-square test was used to test the key secondary endpoint at the 0.05 significance level.

Results

Demographics
Among the 576 patients who entered the IM Depot Stabilization Phase, over half (61%) were male. The mean age was 40 years (range 18-60) with a greater proportion less than age 45 (62%). Over half were Caucasian (58%) but sizeable proportions were comprised of Black (20%) and Asian (18%) patients.

The demographic characteristics of 403 patients in the Double-Blind IM Depot Maintenance Phase are displayed in Table 2 below. The two randomized groups were demographically comparable and similar to the patients who entered the IM Depot Stabilization Phase.

Table 2: Demographic Characteristics of Randomized Patients in the Double-Blind IM Depot Maintenance Phase

Demographic Characteristic	Aripiprazole IM Depot (N = 269)	Placebo (N = 134)	Total (N = 403)
Sex n (%)			
Male	162 (60.2)	79 (59.0)	241 (59.8)
Female	107 (39.8)	55 (41.0)	162 (40.2)
Age (years)			
Mean (SD)	40.1 (11.0)	41.7 (10.5)	40.6 (10.8)
Range	18 - 60	20 - 61	18 - 61
< 45 n (%)	158 (58.7)	82 (61.2)	240 (59.6)
≥ 45 n (%)	111 (41.3)	52 (38.8)	163 (40.4)
Weight (kg)			
Mean (SD)	80.6 (20.4)	84.8 (23.3)	82.0 (21.4)
Range	43.2 - 178.2	43.3 - 178.4	43.2 - 178.4
Height (cm)			
Mean (SD)	169.5 (9.9)	169.6 (10.8)	169.5 (10.2)
Range	140.0 - 206.0	133.0 - 190.0	133.0 - 206.0
BMI (kg/m^2)			
Mean (SD)	28.1 (6.9)	29.5 (7.5)	28.5 (7.1)
Range	15.7 - 58.2	16.9 - 53.3	15.7 - 58.2
BMI n (%)			
< 18.5 (kg/m^2)	6 (2.2)	2 (1.5)	8 (2.0)
18.5 to < 25 (kg/m^2)	96 (35.7)	42 (31.3)	138 (34.2)
25 to < 30 (kg/m^2)	81 (30.1)	39 (29.1)	120 (29.8)
≥ 30 (kg/m^2)	86 (32.0)	51 (38.1)	137 (34.0)
Race n (%)			
Caucasian	152 (56.5)	92 (68.7)	244 (60.5)
Black or African American	59 (21.9)	22 (16.4)	81 (20.1)
Asian	45 (16.7)	13 (9.7)	58 (14.4)
Other	13 (4.8)	7 (5.2)	20 (5.0)
Ethnicity n (%)			
Hispanic or Latino	29 (10.8)	18 (13.4)	47 (11.7)
Not Hispanic or Latino	239 (88.8)	116 (86.6)	355 (88.1)
Unknown	1 (0.4)	0 (0.0)	1 (0.2)
Region n (%)			
US	122 (45.4)	61 (45.5)	183 (45.4)
Non-US	147 (54.6)	73 (54.5)	220 (54.6)
Last dose in IM Depot Stabilization Phase[a] n (%)			
400 mg	246 (91.4)	123 (91.8)	369 (91.6)
300 mg	23 (8.6)	11 (8.2)	34 (8.4)

[a] Last aripiprazole IM depot dose level in the IM Depot Stabilization Phase from the IM depot trial medication records.

Baseline Severity Of Illness

Patients who entered the IM Depot Stabilization Phase had a mean PANSS total score of 59.4 (range 30-80). They had a mean CGI-Severity score of 3.2 (range 1-4).

The patients who entered the Double-Blind IM Depot Maintenance Phase had a mean PANSS total score of 54.5 (range 31-80) and a mean CGI-Severity score of 2.9 (range 1-4), with almost identical means for the two treatment groups.

Patient Disposition

The prespecified interim analysis after approximately 50% of the events had occurred was conducted by the DMC using a data cut-off of June 8, 2010. At that time, 64 events had occurred and 775 patients had been enrolled in the trial. The disposition of patients at the interim analysis for all trial phases and for the Double-Blind IM Depot Maintenance Phase is summarized in Appendix Table 1 and Appendix Table 2 of this review, respectively.

Patient disposition for the final analysis is displayed for all trial phases in Table 3 and for the Double-Blind IM Depot Maintenance Phase in Table 4 below.

Table 3: Patient Disposition By Trial Phase (Final Analysis)

Subjects	Conversion Phase	Oral Stabilization Phase	IM Depot Stabilization Phase	Double-blind, Placebo-controlled Phase	Total
	n (%)				
Screened	-	-	-	-	1025
Screen failure	-	-	-	-	182
Entered	633 (100)	710 (100)	576 (100)	403 (100)	843 (100)
Discontinued	133 (21.0)	134 (18.9)	173 (30.0)	377 (93.5)	817 (96.9)
Completed[a]	NA	NA	NA	26 (6.5)	26 (3.1)
Entered next phase	500 (79.0)	576 (81.1)	403 (70.0)	NA	NA
Analyzed for safety[b]	632 (99.8)	709 (99.9)	576 (100)	403 (100)	NA
Analyzed for efficacy[c]	NA	702 (98.9)	576 (100)	403 (100)	NA
Reasons for discontinuation					
Sponsor discontinued study[d]	54 (8.5)	42 (5.9)	86 (14.9)	237 (58.8)	419 (49.7)
Other reasons	79 (12.5)	92 (13.0)	87 (15.1)	140 (34.7)	398 (47.2)
Lost to follow-up	13 (2.1)	7 (1.0)	11 (1.9)	8 (2.0)	39 (4.6)
Met withdrawal criteria	4 (0.6)	19 (2.7)	8 (1.4)	4 (1.0)	35 (4.2)
Withdrawn by investigator	4 (0.6)	12 (1.7)	9 (1.6)	14 (3.5)	39 (4.6)
Withdrew consent	24 (3.8)	29 (4.1)	29 (5.0)	18 (4.5)	100 (11.9)
Protocol deviation	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.5)	4 (0.5)
AE[e]	11 (1.7)	14 (2.0)	17 (3.0)	14 (3.5)	56 (6.6)
Lack of efficacy with AE[f]	13 (2.1)	7 (1.0)	12 (2.1)	24 (6.0)	56 (6.6)
Lack of efficacy without AE[g]	8 (1.3)	4 (0.6)	1 (0.2)	56 (13.9)	69 (8.2)

[a] Subjects completed the Double-blind, Placebo-controlled Phase, Week 52 visit.

[b] Subjects receiving at least one dose of trial medication in the corresponding phase are included in the safety analysis.

[c] Subjects evaluated for at least one efficacy endpoint in the corresponding phase are included in the efficacy analysis.

[d] Study was terminated early because of positive results of interim analysis.

[e] Adverse event without lack of efficacy (Conversion, Oral Stabilization, and IM Depot Stabilization Phases) or impending relapse (Double-blind, Placebo-controlled Phase).

[f] Lack of efficacy (Conversion, Oral Stabilization, and IM Depot Stabilization Phases) or impending relapse (Double-blind, Placebo-controlled Phase) with an associated adverse event.

[g] Lack of efficacy (Conversion, Oral Stabilization, and IM Depot Stabilization Phases) or impending relapse (Double-blind, Placebo-controlled Phase) without an associated adverse event.

Table 4: Patient Disposition By Randomized Group in the Double-Blind IM Depot Maintenance Phase (Final Analysis)

Subjects	Aripiprazole IM Depot	Placebo	Total
	n (%)		
Randomized	269 (100)	134 (100)	403 (100)
Discontinued	246 (91.4)	131 (97.8)	377 (93.5)
Sponsor discontinued study[a]	179 (66.5)	58 (43.3)	237 (58.8)
Other reasons	67 (24.9)	73 (54.5)	140 (34.7)
Lost to follow-up	5 (1.9)	3 (2.2)	8 (2.0)
Met withdrawal criteria	2 (0.7)	2 (1.5)	4 (1.0)
Withdrawn by investigator	8 (3.0)	6 (4.5)	14 (3.5)
Withdrew consent	14 (5.2)	4 (3.0)	18 (4.5)
Protocol deviation	2 (0.7)	0 (0.0)	2 (0.5)
AE without impending relapse	9 (3.3)	5 (3.7)	14 (3.5)
Impending relapse with AE	11 (4.1)	13 (9.7)	24 (6.0)
Impending relapse without AE	16 (5.9)	40 (29.9)	56 (13.9)
Completed[b]	23 (8.6)	3 (2.2)	26 (6.5)
Analyzed for safety[c]	269 (100)	134 (100)	403 (100)
Analyzed for efficacy[d]	269 (100)	134 (100)	403 (100)

[a] Study was terminated early because of positive results of interim analysis.

[b] Subjects completed the Double-blind, Placebo-controlled Phase, Week 52 visit.

[c] Subjects receiving at least one dose of trial medication in the Double-blind, Placebo-controlled Phase are included in the safety analysis.

[d] Subjects evaluated for at least one efficacy endpoint in the Double-blind, Placebo-controlled Phase are included in the efficacy analysis.

In all, 1025 patients were screened for trial participation and 182 were screening failures, leaving 843 patients to be enrolled in this trial. About one-half (N=419) were withdrawn when the trial was terminated based on the positive results of the interim analysis, with most of these withdrawn from the Double-Blind IM Depot Maintenance Phase (N=237). A total of 403 patients in the Double-Blind IM Depot Maintenance Phase provided efficacy data for analysis (269 patients who received aripiprazole IM depot and 134 who received IM depot placebo).

Concomitant Medication Use
Among the patients randomized, a number took prohibited concomitant antipsychotic medication during the IM Depot Stabilization Phase (Phase 3) or the Double-Blind IM Depot Maintenance Phase (Phase 4). Table 5 displays the number of patients who took such drugs concomitantly.

Table 5: Enumeration of Randomized Patients Who Took Prohibited Antipsychotic Medication

Concomitant Antipsychotic	Phase 4 Randomized Group	
	IM Depot Aripiprazole N=269	IM Depot Placebo N=134
Phase 3		
Haloperidol	0	1
Trifluoperazine	1	0
Phase 4		
Amisulpride	0	1
Aripiprazole	0	7
Haloperidol	0	1
Olanzapine	0	1
Quetiapine	1	0
Quetiapine fumarate	0	3
Ziprasidone	1	1

Given the small number of patients randomized to IM aripiprazole who took a concomitant antipsychotic and the likelihood that the more extensive use in the IM placebo group would have biased the trial results against IM aripiprazole, it seems improbable that this use overall would have biased the efficacy results in favor of IM aripiprazole.

Important Protocol Violations
Three patients were randomized to double-blind treatment in Phase 4 prior to achieving predefined criteria for stability in Phase 3. Two of these were classified as protocol deviations and discontinued from the trial (07246-038-0371 and 07246-048-0804). The third patient (07246-049-0381) experienced two excursions from the stability criteria instead of the one allowed excursion. However, one excursion occurred one day outside the designated time window and, therefore, the patient was considered to be stable and allowed to continue in the trial.

Three patients (07246-001-0001, 07246-012-0096, and 07246-042-0328) were randomized to aripiprazole IM depot but received the 300mg dose in Phase 4 when, in fact, their last dose in Phase 3 was 400mg.

Two subjects (07246-004-0063 and 07246-022-0158) were inadvertently unblinded at the site level. Both patients were prematurely terminated from the

trial and an analysis of the primary endpoint was performed excluding these two patients. Neither experienced an impending relapse event.

Two other subjects (07246-029-0248 and 07246-029-0185) were enrolled in more than one aripiprazole trial and received extra doses of aripiprazole IM depot. They were withdrawn from the trial as soon as their double trial entry was discovered and their data were also excluded from the reanalysis of the primary efficacy endpoint mentioned above.

In addition, three clinical sites were terminated from the trial for cause based on quality assurance audits conducted by Otsuka:

• (b) (4) was terminated due to compliance issues. No patients from this site received study drug in Phase 3 or 4 of the trial.

• (b) (4) was terminated due to significant safety and compliance concerns, particularly suggestions of noncompliance with protocol procedures for administering study drug. None of the patients from this site had been randomized to treatment in Phase 4.

• (b) (4) had significant compliance issues, in particular issues suggesting possible falsification of data by the study coordinator. A total of 13 patients had been enrolled at this site and 7 were assigned to treatment in Phase 4. Analysis of the primary efficacy endpoint excluding these 7 patients were completed by the sponsor and no difference in the results was seen.

Dosing
Table 6 displays the number of patients at each injection during the IM Depot Stabilization Phase who received each IM dose. Generally, most patients received the 400mg dose.

Table 6: Dosing During the IM Depot Stabilization Phase

Injection Number	Number of Patients Receiving Dose		
	300mg	400mg	Total
1st Injection	0	576	576
2nd Injection	34	490	524
3rd Injection	43	431	474
4th Injection	10	87	97
5th Injection	5	57	62
6th Injection	6	36	42
7th Injection	3	22	25
8th Injection	2	10	12
9th Injection	1	1	2

An enumeration of patients by IM dose received at each scheduled injection during the Double-Blind IM Depot Maintenance Phase is displayed in Table 7. Again, the vast majority of patients at each visit received the 400mg dose.

Table 7: Dosing During the Double-Blind IM Depot Maintenance Phase

Injection	Aripiprazole IM Depot (N = 269) Injection Dose		
	Total	400 mg	300 mg
	Ne (%)[a]	n (%)[b]	n (%)[b]
1st Injection	269 (100)	244 (90.7)	25 (9.3)
2nd Injection	223 (82.9)	205 (91.9)	18 (8.1)
3rd Injection	191 (71.0)	174 (91.1)	17 (8.9)
4th Injection	170 (63.2)	152 (89.4)	18 (10.6)
5th Injection	140 (52.0)	126 (90.0)	14 (10.0)
6th Injection	119 (44.2)	106 (89.1)	13 (10.9)
7th Injection	89 (33.1)	79 (88.8)	10 (11.2)
8th Injection	66 (24.5)	60 (90.9)	6 (9.1)
9th Injection	58 (21.6)	51 (87.9)	7 (12.1)
10th Injection	48 (17.8)	43 (89.6)	5 (10.4)
11th Injection	37 (13.8)	32 (86.5)	5 (13.5)
12th Injection	31 (11.5)	27 (87.1)	4 (12.9)
13th Injection	25 (9.3)	23 (92.0)	2 (8.0)

Efficacy Results

The first interim analysis (i.e., after the 63rd case of impending relapse) occurred on June 8, 2010, which was taken as the efficacy cut-off date. A 64th event occurred on this date and so 64 events were included in this interim analysis. The analysis of time to impending relapse, the primary efficacy endpoint, was positive (see Table 8 below). The relapse rate among aripiprazole IM patients was 10% compared to 37% in the placebo IM group. Hence, on July 26, 2010,

the DMC recommended that the sponsor stop the trial. Otsuka concurred with the recommendation and sites were instructed to have all patients return to the clinic for discontinuation and the option to enroll in trial 31-08-248.

The last patient was discontinued from this trial on August 24, 2010. From the June 8 to August 24, 2010, an additional 16 impending relapses occurred. Therefore, the number of relapses in the final analysis was 80. The results of the final primary analysis are consistent with those of the interim analysis and are displayed in Table 8 below. IM placebo patients had a 4-fold greater relapse rate risk of impending relapse than patients receiving IM aripiprazole. Figure 2 presents the survival curves for the final analysis.

Table 8: Interim and Final Analysis Of Time To Impending Relapse

Treatment Group	N Random	N Impending Relapse	Impending Relapse Rate (%)	Median Time to Event (days)	Hazard Ratio	95% CI	P-value[a]
Interim analysis							
Aripiprazole IM depot	230	22	9.6	NE	0.212[b]	0.126, 0.357	< 0.0001
Placebo	114	42	36.8	212	4.72[c]	2.81, 7.94[c]	
Final analysis							
Aripiprazole IM depot	269	27	10.0	NE	0.199[b]	0.125, 0.317[b]	< 0.0001
Placebo	134	53	39.6	209	5.029[c]	3.154, 8.018[c]	

NE = not estimable, Random = randomized.

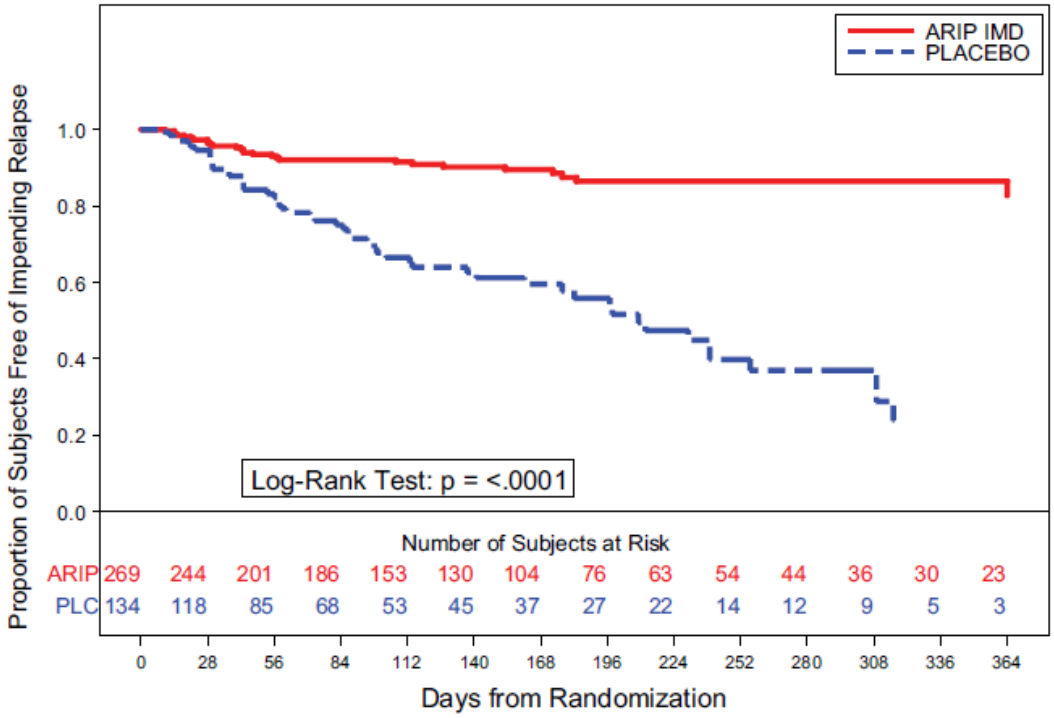
The median time to impending relapse was not estimable because the percentage of subjects in the aripiprazole IM depot group who experienced an impending relapse during the 52-week Double-blind, Placebo-controlled Phase was too low.

[a] P-value was derived from the log-rank test for time to impending relapse.

[b] Aripiprazole IM depot/placebo. Hazard ratio and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. Hazard ratio < 1 is in favor of aripiprazole IM depot group.

[c] Placebo/aripiprazole IM depot. Hazard ratio and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. Hazard ratio > 1 is in favor of aripiprazole IM depot group.

Figure 2: Kaplan-Meier Plot Of Time To Impending Relapse (Final Analysis)



In the final analysis, among the 27 aripiprazole IM depot-treated patients who relapsed, 20 met the CGI+PANSS criteria and 7 met hospitalization criteria for relapse. Only one met CGI-SS criteria and one met violent behavior criteria. Among the 53 placebo IM depot-treated patients, the distribution was similar: 46 met the CGI+PANSS criteria and 5 met hospitalization criteria for relapse. Only one met CGI-SS criteria and four met violent behavior criteria.

The sponsor states that exclusion of patients with potential data issues, as discussed above under *Important Protocol Violations* (i.e., 2 patients who were unblinded, 2 patients who participated in more than one aripiprazole trial, and 7 patients from site 046), had no effect on the primary efficacy results; comparisons remained statistically significant ($p<0.0001$).

A preliminary report of OSI inspection findings from site 002 (Dr. Khan) suggested that that data from this site may not be reliable. Dr. Parfionovas, repeated the primary efficacy analysis excluding site 002 as well as excluding both sites 002 and 046. The results of both reanalyses remained strongly positive ($p<0.0001$).[2]

[2] Dr. Parfionovas conveyed these findings to me in an Email dated April 30, 2012.

6.1.3 Crosscutting Issues

Subgroup Analyses

The sponsor conducted a number of analyses to examine the effect of aripiprazole IM depot versus placebo in the following subgroups:

- geographic region (US vs. non-US).
- gender (male vs. female).
- race (Caucasian vs. non-Caucasian).
- age (<45 years vs. ≥45 years).
- ethnicity (Hispanic or Latino vs. not Hispanic or Latino).
- BMI (≤28 kg/m^2 vs. >28 kg/m^2).

The results of these analyses generally were consistent with those from the entire patient sample, with highly statistically significant differences favoring drug over placebo in each subgroup on the primary endpoint (p<0.0001). However, this was not true for the analysis of race and the analysis of ethnicity.

In terms of race, among non-Caucasian patients, those treated with drug experienced a rate of impending relapse that was similar to those who received placebo (9.4% versus 11.9%, respectively); see Table 9 below. This led to a non-significant difference in the non-Caucasian group. The Caucasian subgroup demonstrated an intergroup difference more typical of that seen in the primary analysis, with a placebo rate was 5 times higher than in the drug group. The reason for low rate of impending relapse among non-Caucasians who received placebo is unknown.

Table 9: Time To Relapse By Race Subgroup

				Arip vs Placebo[a]		Placebo vs Arip[b]		
Treatment Group	N Random	N Impending Relapse	Impending Relapse Rate (%)	Hazard Ratio	95% CI	Hazard Ratio	95% CI	P-value[c]
Caucasian								
Aripiprazole IM depot	152	16	10.5	0.161	0.091, 0.283	6.230	3.532, 10.990	< 0.0001
Placebo	92	48	52.2	-	-	-	-	-
Non-Caucasian								
Aripiprazole IM depot	117	11	9.4	0.680	0.236, 1.960	1.471	0.510, 4.242	0.4720
Placebo	42	5	11.9	-	-	-	-	-

Arip = aripiprazole IM depot; Random = randomized.

[a] Hazard ratio and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. A hazard ratio < 1 is in favor of the aripiprazole IM depot group.

[b] Hazard ratio and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. A hazard ratio > 1 is in favor of the aripiprazole IM depot group.

[c] P-value was derived from the log-rank test for time to exacerbation of psychotic symptoms/impending relapse.

Regarding ethnicity, the rate of impending relapse among Hispanic or Latino patients treated with drug was almost 2-fold higher than that among their non-Hispanic or Latino counterparts, as presented in Table 10 below. Also, the rate of relapse among Hispanic or Latino patients treated with placebo was less than that among non-Hispanic or Latino patients treated with placebo. These factors together produced a non-significant finding in the Hispanic or Latino group. However. drug was numerically superior to placebo. One possible reason for this aberrant finding was the relatively small size of the Hispanic or Latino group, which was about 7-fold smaller than the non-Hispanic or Latino group.

Table 10: Time To Relapse By Ethnic Subgroup

				Arip vs Placebo[a]		Placebo vs Arip[b]		
Treatment Group	N Random	N Impending Relapse	Impending Relapse Rate (%)	Hazard Ratio	95% CI	Hazard Ratio	95% CI	P-value[c]
Hispanic or Latino								
Aripiprazole IM depot	29	5	17.2	0.739	0.213, 2.561	1.353	0.390, 4.690	0.6322
Placebo	18	5	27.8	-	-	-	-	-
Not Hispanic or Latino								
Aripiprazole IM depot	239	22	9.2	0.167	0.101, 0.278	5.980	3.599, 9.936	< 0.0001
Placebo	116	48	41.4	-	-	-	-	-

Arip = aripiprazole IM depot; Random = randomized.

[a] Hazard ratio and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. A hazard ratio < 1 is in favor of the aripiprazole IM depot group.

[b] Hazard ratio and its 95% CI were derived from the Cox proportional hazard model with treatment as a term. A hazard ratio > 1 is in favor of the aripiprazole IM depot group.

[c] P-value was derived from the log-rank test for time to exacerbation of psychotic symptoms/impending relapse.

In addition, for this trial, we had asked the sponsor to examine efficacy data for patients who took the highest recommended dose of oral aripiprazole (30 mg/day) and transitioned to IM depot aripiprazole to determine if the 400mg IM dose provided adequate antipsychotic efficacy in these patients. In particular, we requested the results of the following analyses:

1) for all subjects who were taking a 30 mg/day dose of oral aripiprazole at the end of Phase 2 (Oral Stabilization), entered Phase 3 (IM Depot Stabilization), and had PANSS scores at the final Phase 2 visit and week 2 and week 4 visits of Phase 3, we requested the PANSS total score mean, maximum/minimum, and standard deviation as well as the number of patients on which these calculations were based at each of these three time points. Also, we asked for these statistics at the last Phase 2 assessment and the last available Phase 3 assessment for subjects who were taking a 30 mg/day dose of aripiprazole at the end of Phase 2, entered Phase 3, and dropped out prior to the week 4 assessment in Phase 3.

2) we requested that the sponsor repeat the above analyses for all subjects taking an oral aripiprazole dose less than 30 mg/day at the end of Phase 2.

On April 25, 2012, Otsuka provided the results of these subgroup analyses, which are summarized in Table 11 below. For these calculations, the baseline score was considered to be the last assessment during the Oral Stabilization phase. For patients taking 30 mg/day of oral drug and who had PANSS data at weeks 2 and 4 of the IM Depot Stabilization phase, changes from the end of the Oral Stabilization phase to these visits revealed, on average, only small changes in the PANSS total score. Among dropouts prior to week 4 of the IM Depot Stabilization phase, there was a mean increase in the PANSS score in both the dose groups, with a larger increase in those taking less than 30mg.

Table 11: Mean Changes in the PANSS Total Score Stratified By the Final Dose of Oral Aripiprazole in the Oral Stabilization Phase

Final PO Dose (mg/day)	IM Stabilization Week	N	Mean PANSS at Baseline	PANSS Change from BL
30	2	140	62.08	+0.18
	4	136	61.97	-0.18
<30	2	413	58.24	-0.47
	4	399	58.30	-1.06
Patients Who Dropped Out Prior to Week 4 of IM Stabilization				
30	Last Score	5	66.20	+1.60
<30	Last Score	21	57.62	+3.67

It is notable that the mean baseline PANSS scores in those taking an oral dose of 30 mg/day were higher than those taking lower oral doses, suggesting that those taking the high dose were less responsive.

Key Secondary Variables

The percentage of patients meeting criteria for impending relapse in the final analysis was significantly less among aripiprazole IM depot patients than placebo IM depot patients (10% versus 40%, $p<0.0001$).

Effect Size

The 4-fold reduction in the risk of impending relapse with aripiprazole IM depot compared to placebo is clinically important and compares favorably to the risk reduction observed in a similarly designed trial (CN138-047) with aripiprazole tablets, which showed a 2-fold reduction in relapse risk over 26 weeks of follow-up.

6.1.4 Efficacy Conclusions

Trial 31-07-246 adequately demonstrated that aripiprazole IM depot was superior to placebo IM depot in delaying the time to impending relapse in patients with schizophrenia who had been stabilized on aripiprazole IM depot for at least 12 weeks.

7 REVIEW OF SAFETY

Safety Summary

The review of safety revealed no significant concerns that have not been reported with other formulations of aripiprazole with the exception of injection site reactions, which were mostly mild in severity. Indeed, the safety profile of aripiprazole IM depot is expected to be very similar to that for oral Abilify products, which have been studied extensively over the last decade.

There are no concerns or deficiencies that would preclude approval of this product or require substantial additional labeling.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Deaths, non-fatal serious adverse events, and adverse events that led to dropout were examined in all 8 studies of the development program. Other treatment-emergent adverse events as well as changes in laboratory, vital sign, and ECG parameters were examined from the IM Depot Stabilization phase of the completed Phase 3 trial, 31-07-246.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.1.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data across studies was performed only for the purposes of ascertaining exposure and computing mortality rates. Because of substantial differences in study design and completion status, other pooling of data or trials was not attempted.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As of August 15, 2011, a total of 1190 adult patients with schizophrenia (or schizoaffective disorder in CN138-020) were exposed to aripiprazole IM depot in clinical trials, of which 85 patients were studied in clinical pharmacology trials and 1105 participated in Phase 3 trials.[3] There were 1153 patients who received one or more IM doses of 300mg or 400mg, with a mean exposure of 317.5 days, yielding approximately 1,003 patient-exposure years.

Across all trials as of the above cut-off date, 736 patients received aripiprazole IM depot 300mg or 400mg for 6 continuous months or longer and 231 received injections of 300mg or 400mg for 12 continuous months or longer.

Given that this product produces blood levels of aripiprazole reasonably within the concentration range observed after oral aripiprazole administration at recommended doses and the safety profile of aripiprazole as a molecular entity has been extensively characterized, this exposure is deemed to be adequate for the evaluation of safety.

7.2.2 Explorations for Dose Response

The completed clinical trials with aripiprazole IM depot were not capable of producing reliable data regarding dose dependency of adverse events. The only completed Phase 3 trial, study 31-07-246, did not randomize patients to fixed dose treatment arms and involved prior exposure to oral aripiprazole. Although two Phase 1 trials employed fixed dose arms (31-05-244 and 31-07-002), both were enrolled only a small number of patients and were confounded by oral aripiprazole treatment prior to fixed dose aripiprazole IM depot exposure.

7.2.3 Special Animal and/or *In Vitro* Testing

No special animal or *in vitro* testing was deemed to be necessary.

7.2.4 Routine Clinical Testing

The routine clinical testing of this product included documentation of adverse events and measurement of laboratory parameters, vital signs, and 12-lead electrocardiograms. Additionally, intramuscular injection sites were rated of pain, redness, swelling, and induration. These assessments are considered adequate.

[3] Trials 31-07-247 and 31-08-003 are not included in these figures because both trials remained blinded as of the 120-Day Safety Update cutoff date.

7.2.5 Metabolic, Clearance, and Interaction Workup

The previously conducted metabolic, clearance, and interaction workup applies to aripiprazole IM depot.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Effects on metabolic parameters were evaluated by determining fasting blood concentrations of glucose, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides in the Stabilization Phase of trial 31-07-246.

The measurement of extrapyramidal symptoms (dyskinesia, dystonia, Parkinsonism, and akathisia) was accomplished by ratings on the Simpson-Angus Scale, Abnormal Involuntary Movement Scale, and Barnes Akathisia Rating Scale.

7.3 Major Safety Results

7.3.1 Deaths

As of the cut-off date for the 120-Day Safety Update (August 15, 2011), there were 11 deaths in patients receiving aripiprazole IM depot injections in clinical trials.[4]

I reviewed the narrative summary for each fatal case. These patients generally had multiple predisposing factors that were likely to have significantly contributed to the fatal outcomes. The cases of sudden death merit further description:

• Patient 08248-003-0012 was a 52 year old white male who was found dead in his living room. He had received aripiprazole IM depot 400mg injections over the previous 9 months. Although there was no obvious cause of death and no autopsy was performed, the patient's father stated that the patient suffered with advanced emphysema and was supposed to be on oxygen. Although oxygen and other equipment were found in the patient's apartment, they apparently were not being used. The father also stated that the death certificate indicated that the cause of death was "atherosclerosis cardiovascular disease." Though the cause of death is not clear in this case, the history of emphysema and probable lack of compliance with oxygen therapy as well as the 9 month history of aripiprazole IM depot injections prior to death weigh against attributing the fatal outcome to aripiprazole.

[4] The original submission described only 7 deaths because the outcome of sudden death for one patient (Patient 08248-032-0467) was incorrectly reported as "recovered/resolved." This error was corrected in a subsequent submission dated January 26, 2012, and resulted in a total of 8 deaths as of the January 7, 2011, cut-off date.

• Patient 08248-032-0467 was a 57 year old white male who was found on the floor by his family at home. His medical history was remarkable for diabetes mellitus, hypertension, hyperlipidemia, and erectile dysfunction. Concomitant medications taken within the prior 2 weeks were insulin, cetirizine, benazepril, glimepiride, atorvastatin, sildenafil, vardenafil, vitamin D, and cephalexin. He had gained about 8 pounds over the prior 3 months. His last injection was (b) (6) days prior to death. No autopsy was performed. The death certificate indicates that the death was due to natural causes. The patient's sister stated that he died as a consequence of diabetes.

All patients who died are listed in Table 12.

Table 12:
Deaths Associated With Aripiprazole IM Depot[5]

Study/Patient ID	Age	Sex	Onset (days)[6]	Dose (mg)	Cause of Death
Study 31-07-246					
07246-125-0597	49	M	47	400	Myocardial ischemia
07246-052-0301	50	M	174	400	Pancreatic carcinoma
Study 31-07-247[7]					
07247-450-2670	51	M	103	Blinded	Cardiac arrest
07247-582-2878	44	M	174	Blinded	Suicide
Study 31-08-248					
08248-003-0012	52	M	275	400	Sudden death
08248-024-0252	59	F	73	400	Myocardial infarction
08248-032-0467	57	M	82	400	Sudden death
08248-051-0410	48	M	72	400	Lung cancer
08248-525-2666	38	M	2	400	Ruptured brain aneurysm
08248-554-2652	60	M	77	400	Congestive heart failure
08248-864-4189	54	M	147	300	Myocardial infarction

The exposure-adjusted all-cause mortality rate for aripiprazole IM depot among all patients who received 300mg or 400mg doses (N=1153) was slightly higher than those observed in the initial NDA safety database for aripiprazole tablets in schizophrenia and bipolar disorder Phase 2/3 trials, as shown in Table 13.

[5] There was one death due to leptospirosis during oral aripiprazole treatment in trial 31-08-248.
[6] Number of days from the start of aripiprazole IM depot treatment to the onset of the fatal event.
[7] One death occurred during the screening phase for this study and is not included here.

Table 13: Aripiprazole IM Depot versus Aripiprazole Tablet All-Cause Mortality Rates (MRs)		
	IM Depot	**Tablet[8]**
Number of Deaths	11	22
Total N	1153	4206
Exposure (in patient-years)	1,003	2432.5
Crude MR (%)	1.0	0.5
Adjusted MR (per 1000 patient-years)	11.0	9.0

By contrast, in the Alzheimer dementia trials using oral aripiprazole, where a mortality signal for aripiprazole is known to exist, the crude mortality rate was 7.7% and the adjusted rate was 174 per 1000 patient-years.

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAE's) were defined as those which were fatal, life-threatening, persistently or significantly disabling or incapacitating, required inpatient hospitalization or prolonged hospitalization, a congenital anomaly or birth defect, or other medically significant event that may have jeopardized the subject and required intervention to prevent any of the aforementioned outcomes.

Enumerations of patients who experienced non-fatal SAE's during aripiprazole IM depot treatment (or blinded IM depot treatment) as of August 15, 2011, are displayed for each of the 8 trials in Appendix Table 3 of this review.

My examination of these data revealed no findings suggestive of a safety problem probably caused by aripiprazole IM depot treatment that is not currently labeled for other aripiprazole products. Similarly, there were no new safety signals noted among patients who experienced SAE's during oral aripiprazole therapy.

7.3.3 Dropouts and/or Discontinuations

My examination of the listings of adverse events that led to dropout for each of the 8 trials, as of August 15, 2011, revealed no new safety signals.

In trial 31-07-246, 4.9% (28/576) of patients dropped out of the IM Depot Stabilization Phase because of treatment-emergent adverse events. The only event which led to dropout in greater than 1% of patients was schizophrenia (1.4% or 8/576). However, when other psychotic adverse events which resulted in dropout (paranoid schizophrenia, psychotic disorder, and paranoia) were added to the term "schizophrenia," 2.6% (15/576) of patients dropped out due to

[8] Information from the clinical review of NDA 21-436.

psychosis. Two patients (0.3%) dropped out due to akathisia. Other events led to discontinuation in only one patient: dry mouth, chest pain, injection site pain, irritability, hyperkalemia, ovarian cancer, dyskinesia, somnolence, insomnia, schizoaffective disorder, and allergic dermatitis.

During the Double-Blind IM Depot Maintenance Phase of this trial, 7.1% (19/269) of patients treated with aripiprazole IM depot and 13.4% (18/134) of patients treated with placebo IM dropped out due to treatment-emergent adverse events. The adverse events most commonly resulting in dropout were related to psychosis: as expected, more placebo IM-treated patients dropped out due to a psychosis-related adverse event (10.4% or 14/134) than did aripiprazole IM-treated patients (3.3% or 9/269).[9] Table 14 displays the frequency of dropout due to adverse experiences by MedDRA preferred term and treatment group.

Table 14: Incidence of Discontinuation Due To Adverse Events Trial 31-07-246: Double-Blind IM Depot Maintenance Phase[10]

MedDRA Preferred Term	Aripiprazole IM (N=269) n(%)	Placebo IM (N=134) n(%)
Psychotic disorder	7 (2.6)	8 (6.0)
Schizophrenia	2 (0.7)	5 (3.7)
Suicidal ideation	2 (0.7)	0 (0.0)

7.3.4 Significant Adverse Events

Suicidality

Suicidality (i.e., suicidal ideation and behavior) was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Clinical Global Impression of Severity of Suicide (CGI-SS) during trial 31-07-246. The Columbia-Classification Algorithm of Suicide Assessment (C-CASA) was used to classify potential suicidality events.

The final protocol for this trial (dated November 18, 2009) provided for the administration of the C-SSRS at each visit. However, because the original protocol (dated April 30, 2008) specified that the C-SSRS would be given at baseline and at post-baseline visits only if the CGI-SS score was 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2, some patients did not have a C-SSRS rating at each visit. For these patients, Kelly Posner, Ph.D., of Columbia University and the Research Foundation for Mental Hygiene, conducted a separate analysis of adverse events for potential suicidality according to C-CASA criteria.

[9] Based on pooling the MedDRA terms psychotic disorder, schizophrenia, and paranoia.
[10] Adverse events that led to dropout in only one Aripiprazole IM patient and in no placebo IM patient are: injection site pain, rash, gun shot wound, diabetes mellitus, arthralgia, abnormal dreams, anxiety, and suicidal attempt. Adverse events that led to dropout only in the placebo IM group are excluded.

During the IM Depot Stabilization Phase, one patient (1/576 or 0.2%) reported suicidal ideation as a treatment-emergent adverse event (3107246-001-S0014). Treatment continued and the event resolved.

The mean CGI-SS severity scores were stable over this phase, with minimal change at the last visit (1.00 at baseline, 1.01 at last visit; N=575). Similarly, the mean CGI-SS change scores were relatively stable during this phase (3.98 at baseline, maximum of 4.01 across all visits; N=575).

Few subjects had any baseline (N=9) or post-baseline (N=55) evaluation on the C-SSRS. At baseline, none of the 9 patients had suicidal ideation or behavior. During the IM Depot Stabilization Phase, no patient manifested suicidal behavior on the C-SSRS and 6 of 55 patients (11%) reported suicidal ideation, which was confirmed by a C-CASA classification of "suicidal ideation." Of these 6 patients, 5 endorsed only the "Wish to be dead" item on the C-SSRS. The remaining patient (3107246-001-S0014) endorsed all five items on the Suicidal Ideation part of the C-SSRS.

Thus, the incidence of significant suicidal ideation during the IM Depot Stabilization Phase of this trial was very low, with no reports of suicidal behavior.

Other Significant Adverse Events

I examined the ae.xpt files for trials 31-07-246, 31-08-248, and 31-10-270 to identify any other significant adverse experiences reported with aripiprazole IM depot. Specifically, I looked at the MedDRA preferred terms for all listed adverse events, with particular attention to those which were rated as "severe." I found no events which, in my judgment, represented significant, new safety signals.

7.3.5 Submission Specific Primary Safety Concerns

Injection Site Reactions

Injection site reactions are a potential safety concern with the administration of aripiprazole IM depot. Study medication was injected into the gluteal muscle and injection site assessments were performed at each visit beginning with the first injection of the IM stabilization phase through the post-study follow-up visit of trial 31-07-246. The assessments included investigator ratings of pain, redness, swelling, and induration at the injection site using a four-point scale (ranging from absent to severe) and patient ratings of pain using a visual analog scale (VAS) where 0mm=no pain and 100mm=unbearable pain. Ratings were done both within 30 minutes before injection and one hour after injection. Both investigator and patient ratings were based on the most recent injection, that is, on IM study drug administration days, pre-injection assessments rated the site from the injection four weeks prior and post-injection assessments rated the site from the injection administered that same day; on days when IM study drug was not administered, these assessments were based on the latest injection site.

Tables 15 and 16 enumerate all patients in the single-blind IM stabilization phase by their self-rating of pain and by the investigator injection site assessments, respectively, for the first two injections in this phase. Data from subsequent injections are not presented here because of the relatively small number of patients with follow-up data after the third injection in this study phase; ratings from subsequent injections were not substantially different from those presented below. To include data from patients who prematurely discontinued, the current ratings from the last stabilization phase injection for all patients are also shown.

Table 15: Mean Self-Rated Pain Scores (VAS 0-100)
IM Stabilization Phase (Safety Sample)

Injection#	Time	N	Mean	Min	Max
1st Injection	Current	568	6.1	0	70
	F/U	518	1.1	0	60
2nd Injection	Current	517	4.7	0	75
	F/U	471	1.1	0	98
Last Injection	Current	571	4.9	0	97

Table 16: Enumeration of Patients By Injection Reaction Severity IM Stabilization Phase (Safety Sample)						
Parameter/ Injection #	**Time[11]**	**N-Total**	**N-Absent**	**N-Mild**	**N-Moderate**	**N-Severe**
PAIN						
1st Injection	Current	568	419	140	9	0
	F/U	518	515	3	0	0
2nd Injection	Current	514	382	126	6	0
	F/U	469	463	4	1	1
Last Injection	Current	570	436	120	13	1
SWELLING						
1st Injection	Current	568	536	32	0	0
	F/U	518	518	0	0	0
2nd Injection	Current	514	493	20	1	0
	F/U	469	468	1	0	0
Last Injection	Current	570	543	25	2	0
REDNESS						
1st Injection	Current	568	506	61	1	0
	F/U	518	516	2	0	0
2nd Injection	Current	514	469	45	0	0
	F/U	469	469	0	0	0
Last Injection	Current	570	518	52	0	0
INDURATION						
1st Injection	Current	568	544	24	0	0
	F/U	518	515	3	0	0
2nd Injection	Current	514	493	21	0	0
	F/U	469	466	3	0	0
Last Injection	Current	570	549	21	0	0

Overall, injection site reactions tended to be non-existent or mild in severity. In the double-blind phase, reaction severity was comparable between the aripiprazole IM and placebo IM treatment arms.

[11] The current assessment was done about one hour after injection. The follow-up assessment was done at the next visit during which an injection was given but before that injection.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent adverse event (TEAE's) that were reported by 2% or more of patients in the IM Depot Stabilization Phase of trial 31-07-246 are displayed in Table 17.

Table 17: Treatment-Emergent Adverse Events Reported By 2% or More of Patients in the IM Depot Stabilization Phase of Trial 31-07-246

MedDRA SOC/Preferred Term	Aripiprazole IM Depot (N=576)
Gastrointestinal Disorders	
Diarrhea	2%
Nausea	2%
Vomiting	2%
General Disorders and Administration Site Conditions	
Injection site pain	6%
Investigations	
Weight increased	7%
Nervous System Disorders	
Akathisia	6%
Headache	6%
Somnolence	3%
Tremor	4%
Psychiatric Disorders	
Anxiety	7%
Insomnia	8%
Respiratory, Thoracic, and Mediastinal Disorders	
Cough	2%

Insomnia, anxiety, and increased weight were the most commonly reported TEAE's.

The reporting rates of extrapyramidal symptoms (EPS) during the IM Depot Stabilization Phase were generally low. Specific EPS-related adverse events reported by 1% or more of patients in this phase were akathisia (6.3%), tremor (3.6%), and muscle rigidity (1.0%). A total of 17% (98/576) of the patients received anticholinergics during this phase of the trial, most commonly for Parkinsonism or akathisia. EPS scales (i.e., the Simpson-Angus Scale, the Abnormal Involuntary Movement Scale, and the Barnes Akathisia Rating Scale global score) generally showed very little change from baseline during this part of the trial.

The causal relationship to aripiprazole IM depot cannot be definitively assessed because of the lack of a placebo control group. In addition, it must be borne in mind that these patients were treated with oral aripiprazole prior to entering this phase of the study. Therefore, these data cannot address the emergence of adverse events caused by aripiprazole itself.

7.4.2 Laboratory Findings

In the IM Depot Stabilization Phase of trial 31-07-246, laboratory testing included the following parameters:

Serum chemistry
Alkaline phosphatase, ALT, AST, total bilirubin, calcium, chloride, total cholesterol (fasting and random), CPK, creatinine, glucose (random and fasting), glutamyl transferase, HDL cholesterol (random and fasting), LDH, LDL cholesterol (calculated, random and fasting), potassium, total protein, sodium, triglycerides (random and fasting), BUN, uric acid, insulin (random and fasting), and prolactin.
Hematology
Basophils (% and absolute), eosinophils (% and absolute), hematocrit, hemoglobin, hemoglobin A1C, lymphocytes (% and absolute), monocytes (% and absolute), neutrophils (% and absolute), platelet count, RBC count, and WBC count.
Urinalysis
Urine pH and specific gravity.

During this phase, clinical laboratory tests were performed at weeks 4, 20, and 36.

Examination of the mean changes in these parameters from baseline to last visit revealed only one notable finding: a mean increase in random triglyceride levels of 29 mg/dl (baseline mean=110 mg/dl). However, this was based on a sample of only 16 patients. A much larger sample (N=479) provided fasting triglyceride data and revealed a change of only +1.3 mg/dl (baseline mean=137 mg/dl).

The proportions of patients who met any criterion for a potentially clinically significant (PCS) laboratory abnormality during the IM Depot Stabilization Phase of trial 31-07-246 are displayed in Appendix Table 4 of this review. In the absence of a placebo control group, these data cannot be meaningfully interpreted. Nonetheless, a few of these findings merit some discussion:

• four patients had PCS elevations in ALT (≥3xULN). The highest was 608 U/L, which normalized to 17 U/L on follow-up.
• two patients had PCS elevations in AST (≥3xULN). The highest was 444 U/L and this normalized to 15 U/L on follow-up.

• seven patients had PCS total bilirubin levels (≥2.0 mg/dl). The highest was 3.0 mg/dl. That patient subsequently dropped out and no follow-up value was available. It is noted that six of the seven patients had bilirubin levels above 1.0 mg/dl at baseline for this phase. No patient in this phase of the study had a PCS elevation in AST or ALT in combination with a PCS elevation in total bilirubin. Additionally, no patient in any phase of this study experienced jaundice.
• six patients had PCS decreases in absolute neutrophil counts (≤1,500/μL); three of these patients had counts that met the PCS criterion at baseline. The lowest count was 640/μL which normalized to 3,090/μL on follow-up. The other five counts were 1,240/μL and greater; three of these five had follow-up values, all of which increased.

Treatment emergent adverse events related to glucose metabolism were reported by 0.5% (3/576) of patients during the IM Depot Stabilization Phase. These included increased blood glucose (0.3%), decreased blood glucose (0.2%), and glucosuria (0.2%). The mean change in fasting glucose from baseline to the last value was small, a decrease of 0.72 mg/dl. Among the 337 patients with a normal fasting glucose at baseline (<100 mg/dl), 11 (3.3%) had a high fasting glucose level (≥126 mg/dl) post-baseline during this phase. If a patient experienced a fasting serum glucose of 125 mg/dl or higher and/or had glucose in the urine, a determination of the glycosylated hemoglobin or hemoglobin A1C (HbA1C) ratio was obtained. A total of 58 patients had a HbA1C ratio determination at some point during this phase, with a mean value at last visit of 7.22% (range 4.5% to 15.0%). For the 23 patients who had a baseline HbA1C ratio as well as a post-baseline value, the mean change from baseline was +0.74% (range -2.5% to +4.5%, baseline mean = 8.47%). The American Diabetes Association has established a level of 6.5% or higher as a criterion for diabetes mellitus.[12] The higher ratios here are consistent with the selection of these patients based on abnormal fasting serum glucose or glucosuria, suggesting that the patients tested may be diabetic or at risk for diabetes.

Changes from baseline to last visit in the IM Depot Stabilization Phase in fasting lipid parameters (total cholesterol, LDL, HDL, and triglycerides) were all small and clinically insignificant. Table 18 displays the proportion of patients who had a normal value at baseline and, during this study phase, experienced a shift into the abnormal range for one of these measures.

[12] Executive Summary: Standards of Medical Care in Diabetes-2010. Diabetes Care 2010;33(supp1):S4-10.

Table 18: Proportion of Patients with Normal Baseline Values and Potentially Clinically Relevant Shifts in Lipid Parameters IM Depot Stabilization Phase			
Baseline Value	**Abnormal Cutoff**	**N-tested**	**N-abn (%)**
Total cholesterol			
<200 mg/dl	≥240 mg/dl	313	9 (3%)
LDL			
<100 mg/dl	≥160 mg/dl	206	4 (2%)
HDL			
≥40 mg/dl	<40 mg/dl	364	59 (16%)
Triglycerides			
<150 mg/dl	≥200 mg/dl	330	16 (5%)

The larger proportions of patients with abnormal HDL and triglyceride levels parallel observations from patients taking oral aripiprazole but cannot be fully interpreted without a placebo control arm.

There was one dropout in this study phase due to a laboratory test abnormality: subject 07247-040-0375 was a 45 year old female who experienced hyperkalemia (potassium= 6.0 mEq/L) and an elevation in serum creatinine about one week after her first aripiprazole IM depot injection. A week later, her potassium level increased further to over 7.3 mEq/L. Corrective therapy was not specified but the level normalized (5.2 mEq/L) after another week. A second injection was not given as the patient dropped out of the study due to this finding. The patient was taking an ACE inhibitor (lisinopril) for hypertension. Lisinopril has been associated with hyperkalemia.

7.4.3 Vital Signs

The following vital sign assessments were performed during the IM Depot Stabilization Phase: body temperature, supine pulse and blood pressure, sitting pulse and blood pressure, and body weight. Assessments were done weekly for the first month then every two weeks.

My examination of the mean changes from baseline in each of these measures by visit revealed generally small changes.

During this phase, the mean change from baseline to last visit in body weight was minimal (weight loss of 0.2 kg, N=575). The median change in weight was 0.0kg, with a range of -19.6kg to +19.5kg. There were parallel changes in BMI and waist circumference, with mean changes of -0.1 kg/m^2 and -0.4cm, respectively.

The proportions of patients with potentially clinically relevant changes in vital sign parameters at any time during the IM Depot Stabilization Phase were generally small, as shown in Table 19 below. Approximately equal percentages of patients gained and lost 7% of their body weight.

Table 19: Proportion of Patients with Potentially Clinically Relevant Changes in Vital Signs IM Depot Stabilization Phase

Parameter	Criteria	n-total	N-abn	N/n%
Supine heart rate	Increase ≥15 bpm	575	0	0%
	Decrease ≥15 bpm	575	0	0%
Sitting heart rate	Increase ≥15 bpm	573	1	<1%
	Decrease ≥15 bpm	573	1	<1%
Supine SBP	Increase ≥20 mmHg	575	0	0%
	Decrease ≥20 mmHg	575	2	<1%
Sitting SBP	Increase ≥20 mmHg	573	0	0%
	Decrease ≥20 mmHg	573	3	<1%
Supine DBP	Increase ≥15 mmHg	575	1	<1%
	Decrease ≥15 mmHg	575	3	<1%
Sitting DBP	Increase ≥15mmHg	573	4	<1%
	Decrease ≥15 mmHg	573	1	<1%
Orthostatic Hypotension	Decr in SBP ≥20 mmHg and incr in pulse ≥25 bpm	575	1	<1%
Body weight (kg)	Increase ≥7%	575	40	7%
	Decrease ≥7%	575	38	7%

Treatment emergent adverse events possibly related to orthostatic hypotension occurred in 0.7% (4/576) of patients during the IM Depot Stabilization Phase. These events included abnormal orthostatic blood pressure, postural dizziness, presyncope, and orthostatic hypotension.

No patient dropped out of the IM Depot Stabilization Phase because of a vital sign abnormality.

7.4.4 Electrocardiograms (ECG's)

Twelve-lead ECG's were recorded in triplicate, approximately 5 minutes apart, at weeks 4 and 20 and at the end of the IM Depot Stabilization Phase. A central ECG service was utilized to review all ECG's in order to standardize interpretation.

During the IM Depot Stabilization Phase, the mean changes from baseline in ventricular rate and PR, RR, QRS, QT, QTcB, QTcF, and QTcN intervals were generally small and clinically insignificant.[13]

The incidence of potentially clinically relevant ECG abnormalities during the IM Depot Stabilization Phase is shown in Table 20.

Table 20: Proportion of Patients with Potentially Clinically Relevant Changes in ECG Parameters[14]
IM Depot Stabilization Phase (n_{total}=541)

Parameter	Criterion	N-abn	N/n%
Bradycardia	≤50 bpm & ≥15 bpm ↓	2	0.4%
Sinus bradycardia	≤50 bpm & ≥15 bpm ↓	2	0.4%
Supraventricular premature beat	Present	18	3.3%
Ventricular premature beat	Present	14	2.6%
First degree AV block	PR ≥0.20 sec & ≥0.05 sec ↑	2	0.4%
Second degree AV block	Present	1	0.2%
Right bundle branch block	Present	1	0.2%
Acute or subacute infarction	Present	1	0.2%
Myocardial ischemia	Present	5	0.9%
Symmetrical T-wave inversion	Present	17	3.1%

The frequency of these abnormalities was low, with only three occurring in at least 1% of patients: supraventricular premature beats (3.3%), symmetrical T-wave inversion (3.1%), and ventricular premature beats (2.6%).

The incidence of categorical changes in the QTc interval at any time point during the IM Depot Stabilization Phase are displayed in Table 21. Attribution of these changes to aripiprazole IM depot cannot be established because of the lack of a placebo control arm.

[13] QTcB= $QT/RR^{0.5}$, QTcF= $QT/RR^{0.33}$, and QTcN= $QT/RR^{0.37}$.
[14] Parameters for which there were no patients who met the criteria are not shown.

Table 21: Incidence of Categorical Changes in QTc IM Depot Stabilization Phase		
QT Correction/Change Criterion	**N-evaluated**	**N-meet criterion (%)**
QTcB (msec)		
New onset QTc >500	568	2 (0.4%)
Change in QTc ≥30 but <60	541	34 (6.3%)
Change in QTc ≥60	541	3 (0.6%)
QTcF (msec)		
New onset QTc >500	568	1 (0.2%)
Change in QTc ≥30 but <60	541	21 (3.9%)
Change in QTc ≥60	541	1 (0.2%)
QTcN (msec)		
New onset QTc >500	568	1 (0.2%)
Change in QTc ≥30 but <60	541	25 (4.6%)
Change in QTc ≥60	541	1 (0.2%)

There were no dropouts due to ECG abnormalities in the IM Depot Stabilization Phase.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As noted earlier in this review, the completed clinical trials with aripiprazole IM depot were not capable of producing reliable data regarding dose dependency of adverse events.

In fixed dose clinical trials of schizophrenic patients treated with oral aripiprazole, only somnolence was found to be a dose-related adverse reaction.

7.5.3 Drug-Demographic Interactions

We had asked the sponsor to examine the effect of gender, age, and race on adverse event incidence for each adverse experience reported by at least 5% of aripiprazole patients during the Double-Blind IM Depot Maintenance Phase of trial 31-07-246 and at a rate at least twice the placebo rate. Only one adverse event met these criteria, that is, tremor.

For purposes of these analyses, age subgroups were defined as less than age 45 and age 45 and older and race subgroups were defined as Caucasian and non-Caucasian. The results of demographic subgroup analyses are summarized in Appendix Table 5 of this review. There were no statistically significant differences between strata for any demographic variable.

7.6 Additional Safety Explorations

7.6.2 Human Reproduction and Pregnancy Data

Three pregnancies were reported during trial 31-07-246 and are summarized below.

Subject 07246-002-0041 received one dose of aripiprazole IM depot 400mg prior to having a positive pregnancy test. A normal, full-term, female infant was born by spontaneous vaginal delivery with no complications. The infant was doing well at six months with no delays in developmental milestones.

Subject 07246-132-0624 received two injections of aripiprazole IM depot 400mg prior to receiving a positive pregnancy test. A normal, full-term, male infant was born by spontaneous vaginal delivery with no complications about eight and one-half months after the last injection. Follow-up six months later revealed no health concerns.

Subject 07246-202-0744 was the female partner of a male subject in the trial who became pregnant during the trial and elected to terminate the pregnancy by dilatation and curettage. She recovered without incident.

Marketed aripiprazole products are classified as Pregnancy Category C: developmental toxicity has been observed in animal studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor requested a waiver of requirements for pediatric studies with aripiprazole IM depot based on the following considerations:

- schizophrenia is less common overall in children and adolescents compared to adults. The onset of schizophrenia prior to age 13 is rare, with a prevalence estimated at 1 in 10,000. The estimated prevalence in adolescents (ages 13 through 17 years) is about 0.5%.
- recruiting pediatric patients for a placebo-controlled study may not be feasible because 1) this population is already well controlled with oral treatments so there is little incentive for patients to enroll in a clinical trial with a depot formulation, 2) this population is inherently averse to receiving injections, 3) randomization to placebo may place well-controlled patients at risk for relapse, and 4) ethical concerns may lead to difficulty obtaining IRB approval.
- clinical practice guidelines for the treatment of schizophrenia in children and adolescents recommend the use of oral antipsychotics, with only limited use of depot preparations.
- compliance problems that make a depot formulation attractive in adults are less common in the pediatric population because medication is generally

administered by a parent, guardian, or caregiver. Relapse rates and hospitalization are very low in children and adolescents with schizophrenia.

- relapse rates and psychiatric hospitalization rates are low (less than 10%) in children and adolescents with schizophrenia, especially during the first 6 months of treatment with atypical antipsychotics. Thus, depot antipsychotics would offer no advantage.
- the inherent risks that accompany long-term antipsychotic exposure make depot formulations less palatable in the pediatric population.
- the increased risk of extrapyramidal symptoms with depot antipsychotics precludes use in child and adolescent patients.
- children and adolescents are more aversive to receiving intramuscular injections. Even one injection may lead to a negative perception of treatment and negatively affect future treatment with any antipsychotic.
- children and adolescents have a smaller gluteal muscle mass for injection of depot medication. This may lead to differences in absorption and distribution. Also, the smaller available surface area restricts injection site options, even with rotation of sites.

The Pediatric Review Committee (PeRC) PREA subcommittee granted a full waiver of Pediatric Rule requirements on May 9, 2012.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

As might be expected, there were no reports of overdose with aripiprazole IM depot.

No studies of drug abuse potential, withdrawal, or rebound were conducted as part of the aripiprazole IM depot development program. Although an assessment of discontinuation adverse events would have been possible among patients randomized to placebo in the double-blind phase of trial 31-07-246, assessments for adverse events emerging early in that phase were not conducted often enough to provide reliable data regarding discontinuation phenomena.

7.7 Additional Submissions/Safety Issues

A 120-Day Safety Update to this application was submitted on January 23, 2012, with a data cutoff of August 15, 2011. Information from that submission regarding deaths, non-fatal serious adverse events, and dropouts due to adverse events has been incorporated into previous sections of this review.

8 POSTMARKETING EXPERIENCE

Aripiprazole IM depot has not been marketed in any country. Therefore, there are no postmarketing data for this product.

9 APPENDICES

9.1 Literature Review/References

No literature search was conducted by the sponsor. Since aripiprazole IM depot had not been marketed in any country, no published safety reports or epidemiologic studies were expected.

I conducted a search of the literature on April 27, 2012, for articles which described safety or efficacy findings with the IM depot formulation of aripiprazole. This search utilized PubMed and the search string "aripiprazole depot." Only one article was identified.[15] This article briefly discussed the development of aripiprazole IM depot, with particular focus on the findings from trial 31-05-244 (the Phase 1 multiple dose pharmacokinetic trial). There was a brief mention of trial 31-07-246. No new safety or efficacy findings were mentioned in this article.

9.2 Labeling Recommendations

I conducted a high level review of the labeling proposed by the sponsor and, based on that examination, have two comments:

1) section 6.1, which describes the adverse reaction data from clinical trials with aripiprazole IM depot, is based primarily on experience from the randomized, double-blind phase of trial 31-07-246. As discussed elsewhere in this review, those data having little clinical meaning from a safety perspective because they are based on a highly enriched sample (only patients who experienced adequate effectiveness and tolerability during oral and IM depot aripiprazole treatment were entered into this phase of the study and randomized) and because there was a significant difference in follow-up times between the drug and placebo treatment arms, rendering the typical intergroup comparisons of safety findings of little value. Generally, this section of labeling is based on safety data from one or more randomized, placebo-controlled, parallel group trials in drug-naive patients. Such trials have not been conducted with aripiprazole IM depot, in large part because treatment with IM depot mandates previous exposure to the oral formulation. Nonetheless, with the exception of injection site reactions, it is expected that the nature, frequency, and severity of adverse events associated with this product will be very similar to those observed with oral aripiprazole. Therefore, I recommend that this section of labeling be revised to be based on the adverse reaction information contained in Abilify tablet labeling.

2) section 14, which presents the supporting efficacy findings from trial 31-07-246, ends by discussing changes in the PANSS total score during the randomized, double-blind phase of this trial. Changes in the PANSS total score have not been deemed acceptable as a primary or key secondary efficacy

[15] Park M, et al. Aripiprazole treatment for patients with schizophrenia: from acute treatment to maintenance treatment. Expert Rev Neurother 2011;11(11):1541-1552.

variable in this trial, primarily because of the significant difference in observation times between the drug and placebo treatment arms. This information should be removed.

A more granular examination of labeling will be conducted during scheduled meetings of the entire application review team.

9.3 Advisory Committee Meeting

No advisory committee meeting has been held or is planned for this application.

9.4 Appendix Tables

Appendix Table 1:
Patient Disposition By Trial Phase (Interim Analysis)

Subjects	Conversion Phase	Oral Stabilization Phase	IM Depot Stabilization Phase	Double-blind, Placebo-controlled Phase	Total
	n (%)				
Screened	-	-	-	-	971
Screen failure	-	-	-	-	172
In Screening	-	-	-	-	24
Entered	567 (100)	668 (100)	548 (100)	344 (100)	775 (100)
Discontinued	78 (13.8)	94 (14.1)	83 (15.1)	119 (34.6)	374 (48.3)
Completed[a]	NA	NA	NA	18 (5.2)	18 (2.3)
Continuing	29 (5.1)	26 (3.9)	121 (22.1)	207 (60.2)	383 (49.4)
Entered next phase	460 (81.1)	548 (82.0)	344 (62.8)	NA	NA
Analyzed for safety[b]	566 (99.8)	666 (99.7)	548 (100)	344 (100)	NA
Analyzed for efficacy[c]	NA	648 (97.0)	548 (100)	344 (100)	NA
Reasons for discontinuation					
Sponsor discontinued study[d]	2 (0.4)	5 (0.7)	0 (0.0)	0 (0.0)	7 (0.9)
Other reasons					
Lost to follow-up	13 (2.3)	6 (0.9)	11 (2.0)	9 (2.6)	39 (5.0)
Met withdrawal criteria	2 (0.4)	19 (2.8)	10 (1.8)	5 (1.5)	36 (4.6)
Withdrawn by investigator	4 (0.7)	10 (1.5)	7 (1.3)	12 (3.5)	33 (4.3)
Withdrew consent	23 (4.1)	29 (4.3)	27 (4.9)	16 (4.7)	95 (12.3)
Protocol deviation	3 (0.5)	1 (0.1)	0 (0.0)	1 (0.3)	5 (0.6)
AE[e]	10 (1.8)	14 (2.1)	17 (3.1)	12 (3.5)	53 (6.8)
Lack of efficacy with AE[f]	12 (2.1)	6 (0.9)	10 (1.8)	20 (5.8)	48 (6.2)
Lack of efficacy without AE[g]	9 (1.6)	4 (0.6)	1 (0.2)	44 (12.8)	58 (7.5)

NA = not applicable.

Note: The phases of the trial are referred to in supporting statistical tables as Phase 1 (Conversion Phase), Phase 2 (Oral Stabilization Phase), Phase 3 (IM Depot Stabilization Phase), and Phase 4 (Double-blind, Placebo-controlled Phase).

[a] Subjects completed the Double-blind, Placebo-controlled Phase, Week 52 visit.

[b] Subjects receiving at least one dose of trial medication in the corresponding phase are included in the safety analysis.

[c] Subjects evaluated for at least one efficacy endpoint in the corresponding phase are included in the efficacy analysis.

[d] Includes 6 subjects enrolled at Site 035 who were terminated from the trial for noncompliance reasons (refer to Section 5.8.4), and 1 subject from Site 014 who was terminated from the trial for administrative reasons.

[e] Adverse event without lack of efficacy (Conversion, Oral Stabilization, and IM Depot Stabilization Phases) or impending relapse (Double-blind, Placebo-controlled Phase).

[f] Lack of efficacy (Conversion, Oral Stabilization, and IM Depot Stabilization Phases) or impending relapse (Double-blind, Placebo-controlled Phase) with an associated adverse event.

[g] Lack of efficacy (Conversion, Oral Stabilization, and IM Depot Stabilization Phases) or impending relapse (Double-blind, Placebo-controlled Phase) without an associated adverse event.

Appendix Table 2:
Patient Disposition By Randomized Group in the Double-Blind IM Depot Maintenance Phase (Interim Analysis)

Subjects	Aripiprazole IM Depot	Placebo	Total
	n (%)		
Randomized	230 (100)	114 (100)	344 (100)
Discontinued	57 (24.8)	62 (54.4)	119 (34.6)
Sponsor discontinued study	0 (0.0)	0 (0.0)	0 (0.0)
Other reasons			
Lost to follow-up	6 (2.6)	3 (2.6)	9 (2.6)
Met withdrawal criteria	3 (1.3)	2 (1.8)	5 (1.5)
Withdrawn by investigator	6 (2.6)	6 (5.3)	12 (3.5)
Withdrew consent	12 (5.2)	4 (3.5)	16 (4.7)
Protocol deviation	1 (0.4)	0 (0.0)	1 (0.3)
AE without impending relapse	7 (3.0)	5 (4.4)	12 (3.5)
Impending relapse with AE	9 (3.9)	11 (9.6)	20 (5.8)
Impending relapse without AE	13 (5.7)	31 (27.2)	44 (12.8)
Completed[a]	16 (7.0)	2 (1.8)	18 (5.2)
Continuing	157 (68.3)	50 (43.9)	207 (60.2)
Analyzed for safety[b]	230 (100)	114 (100)	344 (100)
Analyzed for efficacy[c]	230 (100)	114 (100)	344 (100)

[a] Subjects completed the Double-blind, Placebo-controlled Phase, Week 52 visit.

[b] Subjects receiving at least one dose of trial medication in the Double-blind, Placebo-controlled Phase are included in the safety analysis.

[c] Subjects evaluated for at least one efficacy endpoint in the Double-blind, Placebo-controlled Phase are included in the efficacy analysis.

Appendix Table 3: Non-Fatal Serious Adverse Events

Study CN138-020: Enumeration of Patients With Non-Fatal Serious Adverse Events	
SAE (Preferred Term)	**Aripiprazole IM Depot (N_{tot}= 20)**
Suicide Attempt	1
Schizophrenia	1

Study 31-07-002: Enumeration of Patients With Non-Fatal Serious Adverse Events	
SAE (Preferred Term)	**Aripiprazole IM Depot (N_{tot}= 26)**
Schizophrenia	2

Study 31-05-244: Enumeration of Patients With Non-Fatal Serious Adverse Events	
SAE (Preferred Term)	**Aripiprazole IM Depot (N_{tot}= 39)**
Chest Pain	1
Diabetic Ketoacidosis	1
Schizophrenia	1

Study 31-07-246: Aripiprazole IM Depot Stabilization Phase Enumeration of Patients With Non-Fatal Serious Adverse Events[16]	
SAE (Preferred Term)	**Aripiprazole IM Depot (N_{tot}= 576)**
Schizophrenia	9
Paranoid schizophrenia	2
Psychotic disorder	2

[16] The following non-fatal serious adverse events were reported in only one patient in this phase of the trial: anemia, acute myocardial infarction, congestive cardiac failure, chest pain, cholecystitis, gastroenteritis, lobar pneumonia, femur fracture, CPK increased, ovarian cancer, paresthesia, delusion, hallucination, paranoia, and schizoaffective disorder.

Appendix Table 3 (continued)

Study 31-07-246: Randomized, Double-Blind Phase Enumeration of Patients With Non-Fatal Serious Adverse Events On Aripiprazole IM Depot[17]		
SAE (Preferred Term)	**Aripiprazole IM Depot (N_{tot}= 269)**	**Placebo IM Depot (N_{tot}= 134)**
Psychotic Disorder	4	4
Schizophrenia	2	2
Suicidal ideation	2	0

Study 31-07-247: Randomized, Double-Blind Phase Enumeration of Patients With Non-Fatal Serious Adverse Events[18]	
SAE (Preferred Term)	**Blinded Study Drug[19] (N_{tot}= 662)**
Schizophrenia	11
Psychotic disorder	10
Paranoid schizophrenia	3
Pneumonia	3
Suicidal ideation	2
Acute myocardial infarction	2

Study 31-08-003: Randomized, Double-Dummy Phase Enumeration of Patients With Non-Fatal Serious Adverse Events[20]	
SAE (Preferred Term)	**Blinded Study Drug[21] (N_{tot}= 183)**
Schizophrenia	5
Auditory hallucination	2
Suicide attempt	2

[17] The following non-fatal serious adverse events were reported in only one aripiprazole IM depot patient and in no placebo patient during this phase of the trial: gun shot wound, injury, multiple injuries, diabetes mellitus, hyperglycemia, hallucination, and suicide attempt.
[18] The following non-fatal serious adverse events were reported in only one patient: congestive cardiac failure, acute respiratory distress syndrome, neuroleptic malignant syndrome, convulsion, sepsis, disseminated intravascular coagulation, acute renal failure, ovarian fibroma/ adenoma, psychotic behavior, drug abuse, asthma, chronic cholecystitis, perforated appendicitis, chest pain, ankle fracture, radius fracture, fatigue, and agitation.
[19] In this trial phase, patients were randomized in a 2:2:1 ratio to aripiprazole IM depot 400mg, oral aripiprazole 10-30 mg/day with IM depot placebo, or aripiprazole IM depot 50mg.
[20] The following non-fatal serious adverse events were reported in only one patient: depression and inguinal hernia.
[21] In this trial phase, patients were randomized in a 1:1 ratio to aripiprazole IM depot or oral aripiprazole, to be administered under double-dummy conditions .

Appendix Table 3 (continued)

Study 31-08-248: Aripiprazole IM Depot Treatment Phase Enumeration of Patients With Non-Fatal Serious Adverse Events[22]	
SAE (Preferred Term)	**(N_{tot}= 928)**
Psychotic disorder	13
Schizophrenia	13
Paranoid schizophrenia	4
Hallucination	3
Pneumonia	3
Suicide attempt	2
Bronchitis	2

Study 31-10-270: Enumeration of Patients With Non-Fatal Serious Adverse Events[23]	
SAE (Preferred Term)	**Open Label Aripiprazole IM Depot (N_{tot}= 148)**
Psychotic disorder	2

[22] The following non-fatal serious adverse events were reported in only one patient: atrial fibrillation, acute pancreatitis, cellulitis, influenza, intentional overdose, breast cancer, hemangioma of liver, convulsion, adjustment disorder, depression, homicidal ideation, schizoaffective disorder, suicidal ideation, ovarian cyst, asthma, chronic obstructive pulmonary disease, pneumothorax, stomach mass, tremor, syphilis, cholelithiasis, concussion, loss of consciousness, anemia, dyspepsia, hypoglycemia, viral hepatitis, upper gastrointestinal hemorrhage, hallucination, open angle glaucoma, multiple injuries, and aggression.
[23] The following non-fatal serious adverse events were reported in only one patient: schizophrenia and vitello-intestinal duct remnant.

Appendix Table 4: Incidence of Potentially Clinically Significant Laboratory Abnormalities During the IM Depot Stabilization Phase of Trial 31-07-246

Test[a]	Criteria	Aripiprazole IM Depot	
		Ne[b]	n (%)[c]
Chemistry			
Alkaline phosphatase (U/L)	≥ 3 x ULN	565	0 (0.0)
ALT (SGPT) (U/L)	≥ 3 x ULN	565	4 (0.7)
AST (SGOT) (U/L)	≥ 3 x ULN	565	2 (0.4)
Bilirubin, Total (mg/dL)	≥ 2.0 mg/dL	565	7 (1.2)
Calcium (mg/dL)	≤ 8.2 mg/dL	565	0 (0.0)
	≥ 12 mg/dL	565	0 (0.0)
Chloride (mEq/L)	≤ 90 mEq/L	565	3 (0.5)
	≥ 118 mEq/L	565	0 (0.0)
Cholesterol, Total, Fasting (mg/dL)	≥ 240 mg/dL	535	70 (13.1)
CPK, Total (U/L)	≥ 3 x ULN	565	19 (3.4)
Creatinine (mg/dL)	≥ 2.0 mg/dL	565	1 (0.2)
Glucose (mg/dL)	≥ 200 mg/dL	94	1 (1.1)
Glucose, fasting (mg/dL)	≥ 115 mg/dL	536	76 (14.2)
HDL cholesterol, fasting (mg/dL)	≤ 30 mg/dL	535	49 (9.2)
LDL-cholesterol calculation, fasting (mg/dL)	≥ 160 mg/dL	528	61 (11.6)
Lactic dehydrogenase (U/L)	≥ 3 x ULN	563	0 (0.0)
Potassium (mEq/L)	≤ 3.0 mEq/L	565	1 (0.2)
	≥ 5.5 mEq/L	565	9 (1.6)
Sodium (mEq/L)	≤ 126 mEq/L	564	1 (0.2)
	≥ 156 mEq/L	564	0 (0.0)
Triglycerides, fasting (mg/dL)	female ≥ 120 mg/dL male ≥ 160 mg/dL	535	233 (43.6)
Urea nitrogen (mg/dL)	≥ 30 mg/dL	565	0 (0.0)
Uric acid (mg/dL)	female ≥ 8.5 mg/dL male ≥ 10.5 mg/dL	565	5 (0.9)
Hematology			
Eosinophils (%)	≥ 10%	563	6 (1.1)
Hematocrit (%)	female ≤ 32% and 3 point decrease from baseline male ≤ 37% and 3 point decrease from baseline	513	9 (1.8)
Hemoglobin (g/dL)	female ≤9.5% g/dL male ≤ 11.5 g/dL	563	14 (2.5)
Neutrophils, absolute (thous/uL)	≤ 1.5 thous/uL	563	6 (1.1)
Platelet count (cells/uL)	≤ 75000 cells/uL	560	0 (0.0)
	≥ 700000 cells/uL	560	1 (0.2)
White blood count (thous/uL)	≤ 2.8 thous/uL	563	3 (05)
	16.0 thous/uL	563	2 (0.4)
Urinalysis			
Glucose, urine	increase of ≥ 2 units	530	10 (1.9)
Protein, urine	increase of ≥ 2 units	530	1 (0.2)
Other			
Prolactin (ng/mL)	> 1 x ULN	564	23 (4.1)

Ne=number of patient evaluated. n=number of patients meeting criterion.

Appendix Table 5: Effect of Demographic Variables on the Reporting Rate of Tremor During the Double-Blind IM Depot Maintenance Phase of Trial 31-07-246[24]

Gender	**Males**		**Females**	
Treatment	**IM Aripiprazole**	**IM Placebo**	**IM Aripiprazole**	**IM Placebo**
N_{event}/n_{total}	12/162	2/79	4/107	0/55
Mantel-Haenszel Chi-Square p-value = 0.08				
Age	**<45 years**		**≥45 years**	
Treatment	**IM Aripiprazole**	**IM Placebo**	**IM Aripiprazole**	**IM Placebo**
N_{event}/n_{total}	9/158	0/82	7/111	2/52
Mantel-Haenszel Chi-Square p-value = 0.08				
Race	**Caucasian**		**Non-Caucasian**	
Treatment	**IM Aripiprazole**	**IM Placebo**	**IM Aripiprazole**	**IM Placebo**
N_{event}/n_{total}	6/152	2/92	10/117	0/42
Mantel-Haenszel Chi-Square p-value = 0.10				

[24] Mantel-Haenszel Chi-Square p-values were calculated using EpiInfo Version 6 StatCalc.

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/s/

GREGORY M DUBITSKY
05/29/2012

JING ZHANG
05/30/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202971 **Applicant: Otsuka Pharm.** **Stamp Date: Sep 26, 2011**

Drug Name: Aripiprazole extended release suspension for injection **NDA/BLA Type: ORIG-1**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	Not feasible.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	Only one trial.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical Overview.
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: # 31-05-244 Study Title:An Open Label, Parallel Arm, Multiple Dose Tolerability, Pharmacokinetics and Safety Study Sample Size: 11, 16, 14 Arms:200, 300, 400mg Location in submission: M5 section 5332	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 31-07-246 Indication:Maintenance schizophrenia				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	No foreign marketing.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			By Division agreement.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Peds waiver request.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	Not requested.
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Gregory M. Dubitsky Oct 13, 2011

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY M DUBITSKY
10/13/2011

JING ZHANG
10/15/2011